REVIEW ARTICLE

The co-morbidity of anxiety and depression in the perspective of genetic epidemiology. A review of twin and family studies

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ABSTRACT

Background. Co-morbidity within anxiety disorders, and between anxiety disorders and depression, is common. According to the theory of Gray and McNaughton, this co-morbidity is caused by recursive interconnections linking the brain regions involved in fear, anxiety and panic and by heritable personality traits such as neuroticism. In other words, co-morbidity can be explained by one disorder being an epiphenomenon of the other and by a partly shared genetic etiology. The aim of this paper is to evaluate the theory of Gray and McNaughton using the results of genetic epidemiological studies.

Method. Twenty-three twin studies and 12 family studies on co-morbidity are reviewed. To compare the outcomes systematically, genetic and environmental correlations between disorders are calculated for the twin studies and the results from the family studies are summarized according to the method of Klein and Riso.

Results. Twin studies show that co-morbidity within anxiety disorders and between anxiety disorders and depression is explained by a shared genetic vulnerability for both disorders. Some family studies support this conclusion, but others suggest that co-morbidity is due to one disorder being an epiphenomenon of the other.

Conclusions. Discrepancies between the twin and family studies seem partly due to differences in used methodology. The theory of Gray and McNaughton that neuroticism is a shared risk factor for anxiety and depression is supported. Further research should reveal the role of recursive interconnections linking brain regions. A model is proposed to simultaneously investigate the influence of neuroticism and recursive interconnections on co-morbidity.

INTRODUCTION

In the etiology of anxiety and depression both genetic and environmental factors play a role. Two recent meta-analyses obtained heritability estimates between 30 % and 40 % for the liability to major depression (MDD) and anxiety disorders, while the remaining variance in liability

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could be attributed entirely to unique environment (Sullivan *et al.* 2000; Hettema *et al.* 2001*a*). An important issue in the search for etiological factors of anxiety disorders and MDD is the frequent co-morbidity. The results of the Epidemiologic Catchment Area (ECA) Study and the National Comorbidity Survey (NCS) have shown that the occurrence of one anxiety disorder increases the risk of having an additional anxiety disorder [odds ratio (OR) on average 6·7] (Kessler, 1995). The same holds for

Table 1. *Models of co-morbidity [from Klein & Riso, 1993 (KR) and Neale & Kendler, 1995 (NK)]*

KR1/NK1	Co-morbidity due to chance
KR2/NK2	Co-morbidity due to sampling bias
KR3/NK3	Co-morbidity due to population stratification
KR4	Co-morbidity due to overlapping diagnostic criteria
KR5–KR7/NK5–8	Co-morbidity due to multiformity: one disorder is an epiphenomenon of another disorder
KR8/NK9	The co-morbid disorder is a third, independent disorder
KR9/NK4	The pure and co-morbid conditions are different phases or alternative expressions of the same disorder
KR10/NK11	One disorder is a risk factor for the other
KR11/NK10	The two disorders arise from overlapping genetic and environmental etiological processes
NK12	Reciprocal causation

the combination of affective disorders (including dysthymia and mania) and anxiety disorders (OR 7·0) (Kessler, 1995). These increased odds ratios indicate that co-morbidity between anxiety and depression is not only due to chance. Moreover, since the ECA and NCS studies are population based, sampling bias is highly unlikely to explain co-morbidity rates.

The issue of co-morbidity gives rise to questions at a nosological level (Neale & Kendler, 1995). Do anxiety disorders and MDD reflect an arbitrary division of a single syndrome? Are the different anxiety disorders and MDD distinct entities, possibly influenced by common genetic and environmental etiological factors? Are the co-morbid conditions independent of the separate anxiety disorders and MDD? Klein & Riso (1993) presented a comprehensive description of models explaining the causes of co-morbidity (referred to as models KR1–KR11). These models have been partly redefined and extended by Neale & Kendler (1995) (referred to as models NK1–NK12). All models are summarized in Table 1. The relationship between these models and the nosological questions regarding co-morbidity is introduced and discussed below. With respect to chance and sampling bias as possible explanations of co-morbidity, results from the ECA and NCS studies indicate that these factors are unlikely to explain co-morbidity in anxiety and depression. Therefore, these models (i.e. KR1-2/NK1-2) will not be further addressed in this article.

Models KR4 (overlapping diagnostic criteria) and KR5–7/NK5–8 (multiformity) refer to the possibility that the different disorders are distinct entities. Multiformity signifies that co-morbidity is due to disorder B being an epiphenomenon of disorder A. In other words: having disorder A increases the risk that a subject develops disorder B without being vulnerable to disorder B itself. Neale & Kendler (1995) interpreted the description of heterogeneity (KR7) by Klein & Riso (1993) as multiformity in both directions. Thus, disorder B can be an epiphenomenon of disorder A and vice versa. In model KR8/NK9 the co-morbid condition is considered as a third, independent disorder. Model KR9/NK4 supposes that the disorders are all expressions of one disease. In models KR10–11/NK10–12 the disorders are considered to be distinct entities with overlapping etiological processes. In contrast with the multiformity models, in these models vulnerability to one disorder is correlated with vulnerability to the other.

Co-morbidity research: twin and family studies

Cross-sectional data on unrelated individuals cannot discriminate between co-morbidity models. Twin and family data as well as longitudinal data are more suitable for this purpose (Klein & Riso, 1993; Neale & Kendler, 1995). Since the aim of this paper is to investigate the co-morbidity of anxiety disorders and MDD from a genetic epidemiological point of view, the focus will be on twin and family studies. In a twin or family design, two main statistical methods are used to study co-morbidity models, namely (1) biometrical model fitting using twin and/or family data and (2) comparing prevalence rates, odds ratios or relative risks ratios of disorders between relatives of different proband groups.

In twin studies, biometrical model fitting is mostly used to estimate the influences of genetic, common environmental and unique environmental factors on disease liability. Twin studies make use of the fact that monozygotic (MZ) twin pairs share all (or nearly all) their genes, whereas dizygotic (DZ) twin pairs share on

average half of their segregating genes. Consequently, if MZ twin pairs are more similar for a trait than DZ twin pairs this suggests that genetic factors influence this trait. If, on the other hand, MZ and DZ twin pairs show the same amount of similarity, then common environmental factors, shared by family members, probably play a role. The differences between MZ twin pairs are explained by unique environmental factors (for an overview of the methodology of twin studies see Boomsma *et al.* 2002). This univariate design can be extended to a multivariate approach (Heath *et al.* 1993; Duffy & Martin, 1994) in which the correlation between disorders is decomposed partly due to genetic factors shared by these disorders, partly due to shared common environmental factors and partly due to shared unique environmental factors. This approach provides the opportunity to test whether disorders are caused by overlapping genetic or environmental factors (model KR11/NK10). Under certain conditions, this multivariate design can also be used to test models of causality, namely disorder A causes B or reciprocal causation (models KR10/NK11 and NK12 respectively) (Heath *et al.* 1993; Duffy & Martin, 1994). Subsequently, Neale & Kendler (1995) have described how other co-morbidity models can be tested in a twin or family design as well.

Family studies mostly compare prevalence rates, odds ratios or relative risk ratios of disorders between relatives of different proband groups to test co-morbidity models. Klein & Riso (1993) emphasized that, to be able to discriminate properly between the different models, the relatives of four proband groups need to be studied: (1) probands with a pure form of disorder A, (2) probands with a pure form of disorder B, (3) probands with co-morbidity of A and B and (4) controls with neither A nor B. Table 2 shows which patterns of findings can be predicted for each model according to Klein & Riso (1993). The diagnosis in relatives is the dependent variable while the expected ordering of the proband groups is the independent variable (see also Wickramaratne & Weissman, 1993). For example, the predictions for KR4 (overlapping diagnostic criteria) should be read as follows. The chance of having a relative with disorder A is highest in probands with disorder A, followed by probands with disorders AB.

Table 2. *Predictions of co-morbidity models regarding familial transmission [from Klein & Riso, 1993 (KR)]*

Models	Diagnosis in relatives	Relations of proband groups
KR4: overlapping diagnostic criteria	A	A > AB > B = C
	AB	A = AB = B > C
	B	B > AB > A = C
KR5 and KR6: multiformity in one direction	A	A = AB > B = C
	AB	A = AB > B = C
	B	B > A = AB = C
KR7: multiformity in both directions	A	A > AB > B = C
	AB	A = AB = B = C/ AB > A = B > C*
	B	B > AB > A = C
KR8: three disorders	A	A > AB = B = C
	AB	AB > A = B = C
	B	B > A = AB = C
KR9: alternative forms or phases of one disorder	A	A = AB = B > C
	AB	A = AB = B > C
	B	A = AB = B > C
KR10: one disorder is a risk factor for the other	A	A = AB = B > C
	AB	A = AB = B > C
	B	A = AB = B = C
KR11: overlapping etiological processes	A	A = AB > B > C
	AB	A = AB = B > C
	B	B = AB > A > C

* According to Wickramaratne & Weissman (1993).

This chance is not elevated in probands with disorder B when compared with controls. The chance of having a relative with disorder AB is equal in probands with disorder A, AB or B, but elevated when compared to controls. Finally, the chance of having a relative with disorder B is highest in probands with disorder B, followed by probands with disorders AB. This chance is not elevated in probands with disorder A when compared with controls.

Co-morbidity within the perspective of the theory of Gray and McNaughton

Gray & McNaughton (2000) developed a theoretical model about the co-morbidity within anxiety disorders and between anxiety disorders and MDD. In their theory they implement results from animal and psychopharmacological research, which suggest that the disorders are distinct entities, as well as results of genetic research, which suggest overlapping etiologies.

The basis of their theory is that different threat stimuli lead to diverse behavior patterns with emotions regulated by different brain areas. Fig. 1 shows a summary of their theory. First, four different threat stimuli are distinguished: actual and potential threat stimuli which both
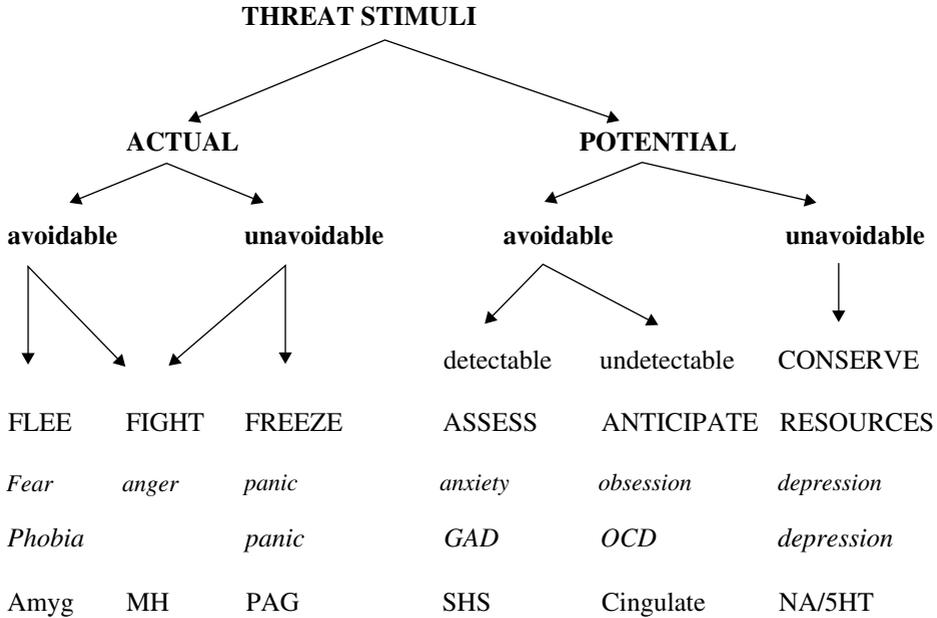
FIG. 1. Nature of stimuli (top three rows) and their relation to function (fourth row), emotion (small italics), psychological disorder (large italics), and principal neural system involved (bottom row). Amyg, amygdala; MH, medial hypothalamus; PAG, periaqueductal grey; SHS, septohippocampal system; NA, noradrenaline; 5HT, 5-hydroxytryptamine. (Reproduced with permission from Gray & McNaughton, 2000, p. 295.)

can be avoidable or unavoidable. These different threat stimuli give rise to activation of particular brain areas resulting in six behavioral reaction patterns with emotions. For example, an avoidable actual threat can lead to activity in the amygdala followed by a flight reaction with fear, whereas an avoidable potential threat can lead to activity of the septo-hippocampal system followed by risk assessment with anxiety. [In this way, Gray & McNaughton (2000) have redefined the terms fear, panic and anxiety as emotions specific to certain circumstances. This differs from the usual definitions.] This part of the theory, mostly based on animal research, provides an explanation of the adaptive reactions to realistic threats. Gray & McNaughton (2000) argue that, at the level of symptoms, there is no fundamental difference between adaptive and pathological emotions, the latter being a consequence of hyperactivity of the same brain regions as the former. They admit that at the syndrome level, it seems a gross oversimplification to align a syndrome to one single brain area, since a syndrome consists of several symptoms. However, they stress that

the various neural structures, which control defensive behavior, are strongly and recursively interconnected. This is necessary since in most real-life situations, the available stimuli will not be selective for just one of the four distinct functional categories. 'The rabbit which sees a fox coming towards it does not necessarily know whether the fox has seen it. Thus, while the presence of the fox is definite and actual, the threat presented by the fox must be treated as having simultaneously the properties of both actual and potential threat. Thus, both fear and anxiety goal-processing systems will be primed for intense action' (Gray & McNaughton, 2000, pp. 296–297). According to Gray & McNaughton (2000), it follows from this example that pathology in a specific control center may give rise to a cluster of symptoms. Subsequently, to relate the symptoms of the DSM III-R anxiety disorders (APA, 1987) to activity in the brain, they reason that fear, panic and anxiety are the core symptoms of respectively simple phobia, panic disorder and generalized anxiety disorder (GAD). In addition, they consider anxiety, and not fear, as

the core symptom of social phobia and agora-phobia, since the supposed threat is potential and not actual.

In this part of the theory, the different disorders are treated as separate entities. The recursive interconnections linking brain regions are hypothesized to explain part of the co-morbidity within anxiety disorders. For example, high levels of anxiety/fear can precipitate panic. Therefore, subjects with agoraphobia or social phobia for whom the threat stimuli are difficult to avoid might develop a panic disorder. On the other hand, panic attacks can, through conditioning, give rise to agoraphobia.

Subsequently, the influence of neuroticism on the development of anxiety disorders is incorporated in the theory. Gray & McNaughton (2000) state that, since neuroticism is a personality trait that is about 50% heritable and related to most anxiety disorders '… there is heritable control over a single, quantitatively varying susceptibility towards suffering from any or all of the neurotic disorders, be they termed panic, anxiety or depression; and this is so irrespective of which particular brain mechanism proximately mediates the symptoms displayed' (p. 342).

To summarize, this theory proposes two mechanisms to explain co-morbidity of anxiety and depression. First, co-morbidity can be caused by recursive interconnections linking the brain regions. This can be interpreted as multiformity in both directions (model KR7/NK5). Second, co-morbidity can be caused by the influence of the heritable personality trait neuroticism, which makes a subject vulnerable to anxiety disorders and MDD. This is equivalent to model KR11/NK10 (overlapping etiological factors). In this paper, the results of twin and families studies are discussed in the light of the theory of Gray & McNaughton (2000).

METHOD

The MEDLINE database was searched for all adult twin and family studies published between 1966 and 2003 containing combinations of the following key words: (1) anxiety, panic disorder, agoraphobia, social phobia, specific phobia, GAD, depression, mood disorders, neurosis, neuroticism, personality (2) genetics, family studies, twin studies.

Twin and family studies were included if causes of co-morbidity were a focus in the analyses. Therefore, it was required that bivariate or multivariate analyses had been carried out. In the family studies that compared prevalence rates, odds ratios or relative risk ratios, few studies included relatives of three proband groups and a control group as recommended by Klein & Riso (1993). Hence, it was decided to include studies with two proband groups plus a control group as well.

In family studies, different methods are used to establish a diagnosis in relatives: family history, direct interview and best-estimate diagnosis based on direct interview, medical records, and family history data. The best-estimate diagnosis is considered to be the most accurate method to collect data (Leckman *et al.* 1982). The overall accuracy of the family history method is relatively poor and subject to several biases (Roy *et al.* 1996). Consequently, studies were excluded that collected data only through the family history method.

Results of studies are summarized as follows. In those studies that have used biometrical model fitting, the correlations of the genetic and environmental factors between disorders are tabulated. In case these correlations were not described in the original article they were calculated from the (standardized) estimates of the variance are explained by the common and specific genetic and environmental factors (for the exact formula see Neale & Cardon, 1992, p. 194). The results of the family studies that compared prevalence rates are described in the same way as Klein & Riso (1993) described the predictions of the different models, thus, with the diagnosis in relatives as the dependent variable and the observed ordering of the proband groups as the independent variable (see Table 2). However, this was hampered by two problems. First, in some studies one proband group did not differ significantly from the other proband groups but did differ from the control group, regarding the prevalence of a disorder in relatives, whereas the other proband groups did not differ from the control group. This outcome is not taken into account by the predictions of Klein & Riso (1993). Second, in some studies proband groups were only compared with controls and not among themselves. Strictly speaking, in these two cases results cannot be

Table 3. *Twin studies on categorical data* (*above solid line*) *and dimensional data* (*below solid line*)

Study	No. of twins and other relatives	Diagnoses	rG	rC†	rE
Sundet *et al.* (2003)*	282 twins, 239 spouses, 306 offspring of twins	Situational fears, illness-injury fears	0·28	—	0·27
		Situational fears, social fears	0·12	—	0·27
		Situational fears, fears of small animals	0·32	—	0·17
		Illness-injury fears, social fears	0·11	—	0·29
		Illness-injury fears, fear of small animals	0·29	—	0·18
		Social fears, fear of small animals	0·13	—	0·18
Chantarujikapong *et al.* (2001)*‡/ Scherrer *et al.* (2000)*	6654 twins	GAD, PD	0·71	—	0·45
Kendler *et al.* (2001c)*	2396 twins	AgP, SocP	0·47	1·00	0·46
		AgP, Animal P	0·69	0	0·30
		AgP, Situational P	0·59	0	0·26
		AgP, Blood/injury P	0·80	1·00	0·34
		SocP, Animal P	0·40	0	0·35
		SocP, Situational P	0·34	0	0·30
		SocP, Blood/injury P	0·46	1·00	0·41
		Animal P, Situational P	0·50	0	0·19
		Animal P, Blood/injury P	0·67	0	0·26
		Situational P, Blood/injury P	0·57	0	0·22
Nelson *et al.* (2000)*	1344 twins	SocP, MDD	1·0	—	0
Kendler (1996)‡/ Kendler *et al.* (1995)*/ Kendler *et al.* (1992a)	1874 twins	P and GAD	0·58	—	0·36
		P and PD	0·95	—	0·26
		P and MDD	0·31	—	0·37
		GAD and PD	0·77	—	0·41
		GAD and MDD/last year MDD	0·86–1·00	—	0·51–0·70
		PD and MDD	0·59	—	0·42
Neale & Kendler (1995)*	2060 twins	MDD, GAD	1	0·41	0·28
Roy *et al.* (1995)	1484 twins	GAD, MD	1	—	0·28
Kendler *et al.* (1993b)	2163 twins	MDD, any P	0·07	—	0·22
		MDD, AgP	0·16	—	0·32
		MDD, SocP	0·11	—	0·12
		MDD, animal P,	0·12	—	0
		MDD, situational P	0	0·09	0·16
Kendler *et al.* (1992b)*	2163 twins	AgP, SocP	0·25	—	0·69
		AgP, Animal P	0·43	—	0·29
		AgP, Situational P	0·24	—	0·49
		SocP, Animal P	0·57	—	0·20
		SocP, Situational P	0·32	—	0·34
		Animal P, Situational P	0·56	—	0·14
Fanous *et al.* (2002)	7542 twins	MDD, Neur	Females: 0·41 Males: 0·68	—	Females: 0·32 Males: 0·33
Ono *et al.* (2002)	402 twins	Dep, Harm avoidance	0·71	—	0·19
Stein *et al.* (2002)	874 twins	Fear of Negative Evaluation, Subscales of Emotional Dysregulation factor	0·49–0·80	—	0·20–0·40
Boomsma *et al.* (2000)*	6426 twins	Anx, Neur	Males: 0·84 Females: 0·85	—	Males: 0·47 Females: 0·51
		Anx, Somatic Anx	Males: 0·76 Females: 0·77	—	Males: 0·26 Females: 0·20
		Anx, Dep	Males: 0·86 Females: 0·74	—	Males: 0·48 Females: 0·54
		Neur, Somatic Anx	Males: 0·71 Females: 0·75	—	Males: 0·40 Females: 0·33
		Neur, Dep	Males: 0·80 Females: 0·71	—	Males: 0·42 Females: 0·43
		Somatic Anx, Dep	Males: 0·73 Females: 0·65	—	Males: 0·29 Females: 0·18
Roberts & Kendler (1999)*	2163 twins	MDD, Neur	0·68	—	0
Gustavsson *et al.* (1996)*	110 twins + 30 MZ reared apart	Psychasthenia, Somatic Anx	1	—	0·29
		Psychasthenia, Psychic Anx	1	—	0·40
		Somatic Anx, Psychic Anx	1	—	0·50

Table 3 (*cont.*)

Study	No. of twins and other relatives	Diagnoses	rG	rC†	rE
Kendler *et al.* (1993*a*)*	1414 twins	Neur time 1, Neur time 2, last year MDD time 2	0·75	—	0·17
Martin *et al.* (1988)*	2903 twins	Neur, heart pounding	Males: 0·93 Females: 0·65	—	Males: 0·21 Females: 0·30
		Neur, feelings of panic	Males: 0·92 Females: 1·00	—	Males: 0·28 Females: 0·48
		Heart pounding, feelings of panic	Males: 0·98 Females: 0·65	—	Males: 0·29 Females: 0·33
Kendler *et al.* (1987)*	5810 twins	6 symptoms of Dep and 7 symptoms of Anx	Males: 0·37–0·99 Females: 38–0·95	—	Males: 0·11–0·70 Females: 0·25–0·86
Phillips *et al.* (1987)	500 twins, 182 siblings, 682 parents	7 Fear factors	0·43–0·89	—	0·17–0·76

AgP, Agoraphobia; Anx, symptoms of anxiety; Dep, symptoms of depression; GAD, generalized anxiety disorder; MDD, major depressive disorder; Neur, neuroticism; P, phobia; PD, panic disorder with or without agoraphobia; SocP, social phobia; rG, correlation between genetic factors; rC, correlation between common environmental factors; rE, correlation between unique environmental factors.

Diagnoses are lifetime unless mentioned otherwise.

* Correlations are calculated based on the (standardized) estimates of the variance explained by the common and specific genetic and environmental factors reported in the articles.

† Dash (–) indicates that in the multivariate analyses common environmental factors were not found to have a significant effect on the disorders under study.

‡ These studies used the same population. Therefore, their results are shown together.

described according to one KR pattern as is required to choose between the different models. To provide the reader with a complete description of the results without losing the opportunity to discriminate between the co-morbidity models, the results are described as follows. It is indicated whether prevalence rates of a disorder in relatives differ between proband groups and controls and, if available, whether prevalence rates of a disorder in relatives differ within proband groups. These results are summarized in one pattern and the KR models that are compatible with this pattern are shown.

Studies have used dimensional and/or categorical data. Dimensional data are measured on a quantitative scale (e.g. Beck Depression Inventory) and are continuous. Categorical data, on the other hand, are mostly based on the DSM categories (APA, 1980, 1987, 1994), leading to dichotomous data, usually affected or unaffected. These results will be discussed separately.

Conclusions about similarities and differences between studies are not based on statistical measures of significance, since no formal meta-analysis was performed.

RESULTS AND CONCLUSIONS FROM TWIN AND FAMILY STUDIES

Twin studies (Table 3)

All twin studies, except Neale & Kendler (1995), tested model KR11 (Table 3). The fit of this model was reasonable in most studies. It should be kept in mind that a high correlation between factors does not imply a strong effect of these factors. For instance, a genetic correlation can be 1, while the variance explained by the shared genes is low, because the two traits have low heritabilities.

Studies that have analyzed categorical data (upper part of Table 3) found that, in general, genetic factors overlap more than unique environmental factors, while common environmental factors generally do not overlap (Kendler *et al.* 1992*a, b*, 1995, 2001*c*; Neale & Kendler, 1995; Roy *et al.* 1995; Kendler, 1996; Nelson *et al.* 2000; Scherrer *et al.* 2000; Chantarujika-pong *et al.* 2001). MDD and GAD appear to be most closely genetically related with the correlation between the genetic factors varying from 0·86–1·00 (Kendler *et al.* 1992*a*, 1995; Kendler, 1996). However, there are a few

exceptions to this general finding. Social phobia seems to share less genetic liability with the other phobic disorders than the other phobic disorders do among each other (Kendler *et al.* 1992*b*, 2001*c*). Furthermore, in females the correlation between the unique environmental factors is mostly larger than the correlation between the genetic factors for the combinations of MDD with phobic disorders (Kendler *et al.* 1993*b*, 1995). As an exception, Nelson *et al.* (2000) did find social phobia and early onset MDD to be completely influenced by the same genes. Differences in age between study populations could explain these divergent findings. Significant overlap in common environmental factors were only found for agoraphobia and social phobia in males (Kendler *et al.* 2001*c*) but not in females (Kendler *et al.* 1992*b*). However, common environmental factors do explain very little variance in these disorders. Finally, results from Kendler *et al.* (1995) on the co-morbidity between MDD, GAD, panic disorder and any phobic disorder suggest that there are two common genetic factors with MDD and GAD loading on one, any phobia loading on the other and panic disorder loading on both.

Studies that have analyzed dimensional data report very comparable results (lower part of Table 3), i.e. in general, genetic factors overlap more than unique environmental factors (Jardine *et al.* 1984; Kendler *et al.* 1987; Phillips *et al.* 1987; Gustavsson *et al.* 1996; Boomsma *et al.* 2000; Sundet *et al.* 2003). Data on neuroticism reveal consistently that neuroticism is genetically related to both depression (measured categorically or dimensionally) and anxiety. Although to a lesser extent, there is overlap in unique environmental factors between neuroticism, depression and anxiety (Jardine *et al.* 1984; Martin *et al.* 1988; Kendler *et al.* 1993*a*; Gustavsson *et al.* 1996; Roberts & Kendler, 1999; Boomsma *et al.* 2000; Fanous *et al.* 2002; Ono *et al.* 2002; Stein *et al.* 2002). No study found an influence of common environment and thus, no significant correlation between common environmental factors either.

As mentioned at the beginning of this paragraph, Neale & Kendler (1995) tried to distinguish between several models of co-morbidity. With respect to the relationship between MDD and GAD, the models of multiformity (NK6), overlapping etiologies (NK10), MDD causing GAD (NK11) and reciprocal causation (NK12) were all found to fit the data. MDD causing GAD seemed to be the best-fitting model.

Family studies

Table 4 shows the results from the family studies that compared prevalence rates, odds ratios or relative risk ratios of different diagnoses in relatives per proband group. The structure of this table is as follows. The column 'probands *versus* controls' show whether the three proband groups, consisting of one group of subjects with disorder A, one group of subjects with disorder B and one group of subjects with the co-morbid condition, are significantly different from controls. The column 'probands *versus* each other' show whether proband groups are significantly different from each other. In other words, do probands with disorder A have more or the same amount of relatives with disorder A han probands with disorder B or than probands with the co-morbid condition. The column 'relations of proband groups' combines the results to subsequently decide which co-morbidity models are compatible with the results.

It becomes clear from the last column that models 4–8 are most often compatible with the results (Weissman *et al.* 1993; Wickramaratne & Weissman, 1993; Goldstein *et al.* 1994; Mannuzza *et al.* 1994; Fyer *et al.* 1995, 1996; Maier *et al.* 1995; Klein *et al.* 2003). Model KR8 (the co-morbid condition is a third disorder) does not seem to be an appropriate explanation, since all combinations of co-morbidity are seen among the anxiety disorders (Kessler, 1995). From a clinical point of view, model KR4 (overlapping diagnostic criteria) is not very probable regarding the co-morbidity between panic disorder and MDD since these disorders do not share most of their diagnostic criteria. With regard to the co-morbidity within the anxiety disorders, model KR4 cannot be excluded as an explanation, according to data from Fyer *et al.* (1995, 1996). However, these results should be interpreted cautiously since the analyses are not performed with the relatives subdivided in groups with mutual exclusive diagnoses. Instead, the group of relatives with disorder A + B is included in the group with disorder A as well as in the group with disorder B. Otherwise there would not have been enough

Table 4. *Family studies, using prevalence rates, odds ratios or relative risk ratios*

Study	N probands (P)/N relatives. N Controls (C)/N relatives	Diagnosis in relatives	Probands *versus* controls				Probands *versus* each other		Relations of proband groups†	Compatible KR models
Klein *et al.* (2003)	P: 345/1432	MDD	MDD>C	MDD+AnxD>C	AnxD=C	MDD=AnxD	MDD=MDD+AnxD	AnxD=MDD+AnxD	MDD=MDD+AnxD>AnxD=C	5 and 6
	C: 352/1176	MDD+AnxD	MDD=C	MDD+AnxD>C	AnxD=C	MDD=AnxD	MDD=MDD+AnxD	AnxD=MDD+AnxD	MDD+AnxD>MDD=AnxD=C	8
		AnxD	MDD=C	MDD+AnxD>C	AnxD>C	AnxD>MDD	MDD=MDD+AnxD	AnxD=MDD+AnxD	AnxD=MDD+AnxD>MDD=C	none
Fyer *et al.* (1996)	P: 118/325	SocP*	SocP>C	SocP+PD=C	PD=C		SocP>SocP+PD	PD=SocP+PD	SocP>SocP+PD=C	8
	C:77/231	PD+SocP	SocP=C	SocP+PD=C	PD=C		SocP=SocP+PD	PD=SocP+PD	SocP=SocP+PD=PD=C	7
		PD*	SocP=C	SocP+PD=C	PD>C		SocP=SocP+PD	PD=SocP+PD	PD>SocP+PD=SocP=C	5 and 6, 8
Maier *et al.* (1995)	P: 280/883	PD	PD>C	MDD+PD>C	MDD=C		PD=MDD+PD	MDD=MDD+PD	PD=MDD+PD>MDD=C	5 and 6
	C:109/409	MDD+PD	PD=C	MDD+PD>C	MDD>C		PD=MDD+PD	MDD=MDD+PD	MDD=MDD+PD>PD=C	5 and 6
		MDD	PD>C	MDD+PD>C	MDD>C		PD=MDD+PD	MDD=MDD+PD	MDD=MDD+PD=PD>C	9
Fyer *et al.* (1995)	P: 103/285	SP*	SP>C		SocP=C	SP>SocP			SP>SocP=C	4–8
	C: 77/231	SocP*	SP=C		SocP>C	SocP=SP			SocP>SP=C	4–8
		SP*	SP>C		PD=C	SP>PD			SP>PD=C	4–8
		PD*	SP=C		PD>C	PD>SP			PD>SocP=C	4–8
		SocP*	SocP>C		PD=C	SocP>PD			SocP>PD=C	4–8
		PD*	SocP=C		PD>C	PD>SocP			PD>SocP=C	4–8
Mannuzza *et al.* (1994)‡	P: 126/347	MDD		MDD+PD>C	PD=C			PD=MDD+PD	MDD+PD>PD=C	4–7
	C: 77/231	MDD+PD		MDD+PD>C	PD=C			MDD+PD>PD	MDD+PD>PD=C	5 and 6, 8
		PD		MDD+PD=C	PD>C			PD=MDD+PD	PD>PD+MDD=C	5 and 6, 8
Goldstein *et al.* (1994)‡/	P: 148/792	PD	PD>C	PD+MDD>C	MDD**=C				PD≥PD+MDD>MDD**=C	4–7
Weissman *et al.* (1993)/	C: 45/255	PD+MDD	PD>C	PD+MDD>C	MDD**>C				PD≥PD+MDD≥MDD**>C	4, 7, 9–11
Wickramaratne & Weissman (1993)		MDD**	PD=C	PD+MDD>C	MDD**>C				MDD**≥PD+MDD>PD=C	4, 7

AnxD, anxiety disorders; GAD, generalized anxiety disorder; MDD, major depressive disorder; P, phobia; PD, panic disorder with or without agoraphobia; SocP, social phobia.
* Diagnoses include the co-morbid condition.
** MDD with age of onset <30 years.
† This column shows a summary of the results shown in the columns probands *versus* controls and probands *versus* each other and is comparable with the last column in Table 2.
‡ These studies used the same population. Therefore, their results are shown together.

Table 5. *Family studies, using biometrical model fitting*

Study*	No. of relatives	Diagnoses	rF	rE
Sham *et al.* (2000)*	5909 sibs	Neuroticism, high positive affectivity	−0·65	−0·29
		Neuroticism, anxious arousal	0·70	0·21
		High positive affectivity, anxious arousal	−0·70	−0·40
Merikangas *et al.* (1994)/Leckman *et al.* (1983)‡	Probands: 133/810 Controls: 82/521	MDD, anxiety disorders	0·99	0
Tambs (1991)*	814 fathers, 880 mothers, 564 siblings	Anx/Dep	0·77	0·27

rF, Correlation between familial factors; rE, correlation between unique environmental factors; Anx, symptoms of anxiety; Dep, symptoms of depression; MDD, major depressive disorder.

* Correlations are calculated based on the (standardized) estimates of the variance explained by the common and specific genetic and environmental factors reported in the articles.

‡ These studies used the same population. Therefore, their results are shown together.

power for statistical analyses due to the low number of relatives with the co-morbid disorder. This leaves models KR5–KR7 (multiformity) as the most likely options to explain the co-morbidity between MDD and anxiety disorders and possibly also within the anxiety disorders. Klein *et al.* (2003) have studied the co-morbidity between MDD and all anxiety disorders. Their results are incompatible with any of the KR models. They conclude that their results are compatible with an independent familial transmission of the disorders with co-morbidity caused by non-familial etiological factors.

Table 5 shows the outcomes of the family studies that, similar to the twin studies, have used biometrical model fitting and tested the hypothesis that different disorders or traits arise from overlapping etiological processes (KR11/NK10) (Leckman *et al.* 1983; Tambs, 1991; Merikangas *et al.* 1994; Sham *et al.* 2000). In contrast to the other family studies, they conclude that a single common familial factor accounts for a substantial proportion of the covariances between depression and anxiety and neuroticism.

To summarize, the results of the family studies mostly indicate multiformity as a possible explanation for the co-morbidity both within anxiety disorders and between anxiety disorders and MDD, but the model of overlapping etiology could also fit the data.

DISCUSSION

The results of the twin and family studies indicate that the anxiety disorders and MDD are distinct entities and not alternative phases of one disease. The results also rule out that the co-morbid condition is a third disorder. According to the twin and family studies, which used biometrical model fitting, overlapping etiological factors explain the co-morbidity within anxiety disorders and between anxiety disorders and MDD. This common background could, to some extent, be explained by neuroticism since both anxiety and depression do share etiological factors with neuroticism. In general, there is substantial overlap among the genetic factors. Shared unique environmental factors explain a smaller part of the co-morbidity. Common environment tends not to explain variance in anxiety, depression or neuroticism and cannot contribute to co-morbidity between these traits. However, according to most family studies that compared prevalence rates, co-morbidity between MDD and panic disorder and within the anxiety disorders is best explained with the multiformity models.

Before considering these conclusions in the light of the theory of Gray & McNaughton (2000), possible causes of the discrepancy in the results will be discussed. The different approaches that are used by the twin and family studies investigating co-morbidity seem a first possible explanation, since the different results coincide with the different methods. Two simulation studies testing the validity of the KR predictions and the NK model-fitting approach revealed that the latter method was more valid to discriminate the correct co-morbidity model (Rhee *et al.* 2003, 2004). The predictions of Klein & Riso (1993) did not seem to be valid under some circumstances (Rhee *et al.* 2003). In addition, another drawback of the family

studies comparing prevalence rates is that the predictions of Klein & Riso (1993) do not consider that co-morbidity can be explained by non-familial etiological factors (Klein *et al.* 2003). Twin and family studies using biometrical model fitting do take this possibility into account.

However, a major limitation of the twin studies is that they only tested model NK11 and left the other models out of consideration. The simulation study has shown that when using biometrical model fitting, it is difficult to discriminate within and between the classes of multiformity (KR5–7/NK5–8) and overlapping etiology models (KR10–11/NK10–12) (Rhee *et al.* 2004). This is supported by Neale & Kendler (1995), who tested all co-morbidity models on MDD and GAD and found that three overlapping etiology models as well as one multiformity model fitted their data. Therefore, when model KR11/NK10 fits the data, this does not exclude the possibility that another overlapping etiology model (KR11/NK10 and NK12) or multiformity model (KR5–7/NK5–8) fits as well.

Another reason for the discrepant findings between twin and family studies could be that different diagnoses are analyzed. With the exception of Klein *et al.* (2003), the family studies that assessed mutual exclusive diagnoses in the probands as well as the relatives focused on MDD and panic disorder (Weissman *et al.* 1993; Wickramaratne & Weissman, 1993; Goldstein *et al.* 1994; Mannuzza *et al.* 1994; Maier *et al.* 1995), whereas just one twin study investigated these disorders (Kendler *et al.* 1995).

Finally, discrepancies in the findings between family and twin studies could be caused by differences in the study populations. Family studies mostly use clinical populations, while twin studies are most often population based. When family history influences help-seeking behavior, this could bias the results. However, this does not seem to play an important role since the studies that used biometrical model fitting with a clinical population found equal results, i.e. that model KR11 fitted the data (Merikangas *et al.* 1994; Roy *et al.* 1995).

Regarding the theory of Gray & McNaughton (2000), this review agrees that the anxiety disorders and MDD are distinct entities. Given the

methodological issues, the current results are not conclusive as to whether co-morbidity is due to overlapping etiology, probably expressed as the personality trait neuroticism (KR11/NK12), multiformity because of neural recursive interconnections (KR5–7/NK5–8) or both. However, since model KR11/NK12 fits the data in 23 twin and three family studies, the hypothesis that overlapping genetic etiological factors are of importance seems to be supported. This would imply that future research aiming to find genes underlying the vulnerability for anxiety and depression could pool subjects with these disorders. Another possibility would be to search for the genes underlying neuroticism. Environmental risk factors, on the other hand, seem to differ between anxiety and depression. Therefore, subjects with different disorders should be studied separately when these risk factors are investigated. An example of the latter is a recent study on life events as predictors of MDD, GAD or the co-morbid condition (Kendler *et al.* 2003). It appeared that loss and humiliating events were strongly linked to risk for depressive episodes, loss and danger events were linked to risk for generalized anxiety and that the sum of those events preceded mixed anxiety and depression.

It is recommended for future twin and family studies on co-morbidity of anxiety and depression to test all models. However, when all these models are tested separately, it is still impossible to decide whether one specific model or the combination of the two models of overlapping etiological factors and multiformity explain the co-morbidity. Therefore, we propose an additional model. Since it seems likely that neuroticism is the personality trait underlying all these disorders, neuroticism should be included in the analyses as a factor explaining part of the covariance. Subsequently, the co-morbidity models can be tested on the residual covariance of the disorders not due to neuroticism. When the theory of Gray & McNaughton (2000) is right, the best-fitting model will include neuroticism explaining part of the covariance with the residual covariance explained by multiformity in both directions. Yet, this model does not completely cover the theory of Gray & McNaughton (2000) either. Therefore, three latent factors, namely fear, panic and anxiety should be included in the model too. Two factor

analyses on epidemiological data have already shown that MDD, dysthymia and GAD load on an 'anxious misery' factor and the other anxiety disorders load on a 'fear' factor. In turn, the anxious misery factor and the fear factor loaded on an internalizing factor (Krueger, 1999; Vollebergh *et al.* 2001). By adding a third 'panic' factor to the model, the theory of Gray & McNaughton (2000) could be tested.

There are several other issues that need some attention when investigating co-morbidity. To test causal relations properly in twin and family studies, information on the time sequence of disorders is necessary (Goldberg & Ramakrishnan, 1994). Mood disorders, for example, tend to be secondary when co-morbid with anxiety disorders (De Graaf *et al.* 2003). This suggests that anxiety disorders are not an epiphenomenon of MDD and are probably not caused by MDD in most cases. This also applies to studies investigating the relation between neuroticism and anxiety and depression. Findings from the Munich Vulnerability Study, suggest that neuroticism is a risk factor for MDD, since one third of the still healthy, adult relatives of patients with an affective disorder have increased neuroticism scores (Krieg *et al.* 2001). However, several studies have shown that current or past MDD also leads to increased scores of neuroticism (Kendler *et al.* 1993*a*; Duggan *et al.* 1995; Ouimette *et al.* 1996; Farmer *et al.* 2003).

The possible effect of age or sex on causes of co-morbidity should also be considered. Interestingly, the results of Wickramaratne & Weissman (1993) and Weissman *et al.* (1993) suggest that a different model might explain co-morbidity in late-onset MDD (after 30 years). If only relatives with MDD with disease onset after 30 years are considered, no differences are found between the proband groups. This might indicate that late-onset MDD is less familial (Weissman *et al.* 1993; Wickramaratne & Weissman, 1993). Furthermore, in univariate analyses, some studies have indicated that genes influencing neuroticism, anxiety and depression are not entirely the same in men and women (Jardine *et al.* 1984; Kendler *et al.* 1987, 2001*a*; Kendler & Prescott, 1999; Fanous *et al.* 2002) and that heritability of neuroticism, anxiety and depression is higher in women than in men (Jardine *et al.* 1984; Bierut *et al.* 1999; Boomsma

et al. 2000; Kendler *et al.* 2001*a*). However, other studies have found no difference between sexes (Roy *et al.* 1995; Hettema *et al.* 2001*b*; Kendler *et al.* 2001*b*; Ono *et al.* 2002). It remains to be tested whether different models explain co-morbidity in females and males.

In conclusion, this review shows that, as proposed by Gray & McNaughton (2000), anxiety disorders and MDD are distinct disorders with co-morbidity probably partly explained by shared genetic factors which also influence neuroticism. Whether neural recursive interconnections also play a role remains to be investigated. Future co-morbidity research should include testing of various co-morbidity models. Finally, to be able to decide whether either one or two models play a role (i.e. overlapping etiology as well as multiformity), a model should be tested that specifically includes neuroticism.

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DECLARATION OF INTEREST

None.

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