

## Neuroticism as a Genetic Marker for Mood and Anxiety

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### MOOD AND ANXIETY DISORDERS

Almost one in five people will experience a significant mood or anxiety disorder at some stage in life. The lifetime prevalence rates of *Diagnostic and Statistical Manual of Mental Disorders*, third edition, revised (DSM-III-R) mood and anxiety disorders are shown in Table 11.1. As can be seen, the lifetime prevalence of major depression is almost twice as high for females as for males, and this is a robust finding in the literature (Blazer, Kessler, McGonagle, & Swartz, 1994; Breslau, Schultz, & Peterson, 1995; Kendler & Prescott, 1999; Newman, Bland, & Orn, 1988; Parker & Hadzi-Pavlovic, 2001).

Anxiety disorders represent the most common comorbid diagnoses (Sander, Beck, & Beck, 1990). Like that of mood disorders, the prevalence of anxiety disorders is higher among females (Kessler et al., 1994). When based on the DSM-III-R, the lifetime prevalence for generalized anxiety disorder (GAD) in the United States is 3.6% for males and 6.6% for females.

In reality, the prevalence rates for mood and anxiety disorders in Table 11.1 are somewhat different, and often these will differ widely even when they are based on structured clinical interviews. Apart from issues of reliability and accuracy of psychiatric classification, the major sources of discrepancy are varying definitions. For instance, Kendler, Neale, Kessler, Heath, and Eaves (1992d) blindly assessed a population-based sample of 1033 same-sex female twin pairs who were administered a structured psychiatric interview contain-

TABLE 11.1. Lifetime Prevalence Rates (%) of DSM-III-R Mood and Anxiety Disorders

DSM-III-R disorder	Males	Females
<u>Mood disorders</u>		
Major depressive episode	12.7	21.3
Manic episode	1.6	1.7
Dysthymia	4.8	8.0
Any mood disorder	14.7	23.9
<u>Anxiety disorders</u>		
Panic disorder	2.0	5.0
Agoraphobia without panic	3.5	7.0
Social phobia	11.1	15.5
Simple phobia	6.7	15.7
Generalized anxiety disorder	3.6	6.6
Any anxiety disorder	19.2	30.5

*Note.* Data from Kessler et al. (1994).

ing nine commonly used definitions of major depression. As is shown in Table 11.2, depending on the definition, the lifetime prevalence rates for major depression ranged from 12% to 33%. The broadest criteria (DSM-III, Research Diagnostic Criteria [RDC] probable, and DSM-III-R) have the highest prevalence rates of 31% to 33%. Intermediate criteria (Washington University Criteria [WUC] primary and secondary definite, RDC definite, and the Gershon) have prevalence rates of 20% to 25%. The lowest prevalence rates of 12% to 15% come from diagnoses based on the narrowest definitions

TABLE 11.2. Lifetime Population Prevalence of Major Depression as a Function of Diagnostic Criteria

Definition	Prevalence	A	C	E
DSM-III	33%	.39	—	.60
RDC (probable)	32%	.39	—	.61
DSM-III-R	31%	.42	—	.58
WUC	25%	.33	—	.64
RDC (definite)	23%	.44	—	.56
Gershon	23%	.45	—	.55
WUC (primary and secondary definite)	20%	.33	—	.64
WUC (probable)	15%	.21	—	.75
WUC (definite)	12%	.24	—	.73

*Note.* A, C, and E, proportion of variance attributable to additive genetic, shared environmental, and nonshared environmental variance, respectively. RDC, Research Diagnostic Criteria; WUC, Washington University Criteria. Data from Kendler, Neale, Kessler, Heath, and Eaves (1992d).

(WUC probable and definite). Unlike the data for major depression, no data are available that detail the impact of varying definitions on the lifetime population prevalence of anxiety disorders in the United States.

## PREVAILING AND ALTERNATIVE TAXONOMIES OF PSYCHOLOGICAL DISTRESS

The *Diagnostic and Statistical Manual of Mental Disorders* (DSM), published by the American Psychiatric Association (1980, 1987, 1994, 2000), remains one of the most popular diagnostic tools for assessing mental disorders. Unfortunately, it is beyond the scope of this chapter to review the limitations of categorical taxonomies; these are reviewed elsewhere (Eysenck, 1986, 1994b; Kirk & Kutchins, 1992; Millon, 1991; Neale, Eaves, & Kendler, 1994, p. 248; Zuckerman, 1999). Categorical models of classification *are* appropriate if the phenotype is indeed discontinuous. For instance, a categorical model would be useful if a psychiatric disorder could be best explained in terms of a single gene of large effect with or without reduced "penetrance" (which is the likelihood that a given gene will result in disease), or perhaps by some form of discrete environmental transmission, such as a bacterium or virus (Eaves, Eysenck, & Martin, 1989).

## CONTINUOUS-LIABILITY MODEL

Despite the convenience of using measures with dichotomous outcomes, in reality behaviors and traits of biomedical interest more often represent syndromes of numerous physical, behavioral, and psychiatric symptoms, which are more likely to demonstrate continuous than discrete variation. Although Pearson's work laid much of the foundation for 20th-century statistics (e.g., correlation, regression, and standard deviation), it was Fisher who introduced what is now referred to as the "polygenic model." According to this model, an observed phenotype is caused by a large number of genes or genetic loci, each with small effect, acting additively, and inherited according to strict Mendelian laws.

Polygenic models assume that variation within an observed phenotype is caused in part by segregation of a number of genes with small effect. Therefore, as the number of loci influencing a trait increases, the number of separate phenotypic categories increases, and the overall distribution of classes or categories approaches normality. Superimposed upon this genetic variation are environmental effects, which blur the demarcation between individual classes. This causes the overall distribution to appear continuous. In other words, the distribution can be explained in terms of a continuous variable or "liability," which is determined by genetic *and* environmental factors, thereby making the system multifactorial (Fraser, 1976).

Based on empirical evidence outlined elsewhere (Eaves et al., 1989; Eysenck, 1953; Falconer, 1963), the measures of psychological distress and personality discussed in this chapter assume a continuous-liability distribution. Regardless of whether the data are continuous or ordinal, this model assumes that liability to psychological distress or variation in measures of personality arise from the independent action of a large number of factors, each with small effect, which give rise to a normal distribution of liability (Falconer, 1963). The implicit goal in exploring the genetic etiology of psychological distress is to quantify the genetic and environmental sources of variation in the liability, rather than to focus on the dichotomies or thresholds per se.

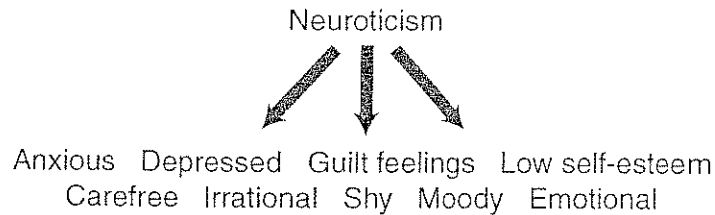
## A PERSONALITY AND INDIVIDUAL-DIFFERENCES APPROACH

Eysenck argued that the best way to understand mechanisms is to study human individual differences. His chief contribution to psychology was his dimensional model of personality, which presents an alternative to categorical ways, with a quantitative and dimensional representation of human behavior (Eysenck, 1967, 1971b; Eysenck & Rachman, 1965).

Eysenck's theory is based on the Galen-Kant-Wundt scheme, which is strongly rooted in the ancient Greek dimensions of "choleric," "sanguine," "phlegmatic," and "melancholic" humors (Eysenck & Eysenck, 1991). The three orthogonal dimensions of "psychoticism," "extraversion," and "neuroticism," which are independent of intelligence, have consistently emerged as second-order factors or superfactors from large-scale factor-analytic studies (Eysenck, 1971b; Eysenck & Eysenck, 1985, 1991). Each superfactor represents a polygenic and hierarchical phenotype, which forms a continuum based on a number of first-order traits. These traits are empirically derived, are intercorrelated, and in turn give rise to the superfactors above them. The superfactors are based on correlational and factor-analytic methods relying on data from self-report questionnaires, peer and observer ratings, miniature situational studies, experimental psychology, psychological measures, and hormonal and biochemical assays—all of which assume a dynamic and causal aspect that relates behavior to fundamental biological factors (Eysenck, 1971b; Eysenck & Eysenck, 1975, 1985).

### Neuroticism

The central focus of this chapter is on neuroticism, and our aim is to demonstrate that individuals with neurotic personalities, in certain environmental circumstances, are highly predisposed to mood and anxiety disorders. An important point is that high scores on neuroticism do not necessarily equate to neurosis. This dimension was originally conceptualized by Eysenck as a quan-



**FIGURE 11.1.** Neuroticism and underlying first-order correlated traits. From Eysenck and Eysenck (1985). Copyright 1985 by Eysenck and Eysenck. Adapted by permission.

titative personality trait defined as an individual's vulnerability to various neurotic disorders and psychological distress (Eysenck, 1953, 1967). It is reliably measured by self-report and is highly stable over time (Eysenck & Eysenck, 1991; Gillespie, Evans, Wright, & Martin, 2004; Kirk et al., 2000). In terms of factorial invariance, the same dimension is identifiable in a diverse range of cultures worldwide and across the socioeconomic spectrum (Eysenck & Eysenck, 1983). Moreover, it has emerged in every model of personality based on questionnaire measurement and analyses of ratings of psychiatric symptoms where anxiety and depression have emerged as general dysphoric or negative effect factors (Zuckerman, 1999; Zuckerman, Kuhlman, Joireman, Teta, & Kraft, 1988).

The hierarchical and behavioral consequences of this personality dimension are summarized in Figure 11.1. As with the other dimensions, the first-order traits are measured dimensionally. High scorers are described as anxious, worrying, moody, and frequently depressed (Eysenck & Eysenck, 1991). When high neuroticism is combined with high extraversion, such individuals are likely to be touchy and restless, easily excitable, and even aggressive. Low scorers, on the other hand, are usually calm, even-tempered, controlled, and unworried.

### Psychobiology of Neuroticism

Eysenck and Eysenck (1985) argued that neuroticism has a constitutional basis with predictable behavioral consequences. Although he insisted that neurotic disorders can be learned, unlearned, extinguished, and treated with behavioral interventions (Eysenck, 1960; Eysenck & Rachman, 1965), he rejected any behavioral explanation of neuroticism or neurosis that did not acknowledge the underlying biological mechanisms.

Constitutionally, the dimension reflects an inherited lability of the autonomic nervous system (including the amygdala, hippocampus, septum, cingulum, and hypothalamus), which controls autonomic activation and the expression of emotion. Emotional stability–instability is characteristic of the

sympathetic-parasympathetic balance within the autonomic nervous system. For this reason, high scores on neuroticism are associated with greater autonomic activation as measured by skin conductance, muscular tension, heart rate, blood pressure, electroencephalogram, and breathing (Eysenck, 1991; Eysenck & Eysenck, 1985).

## CLONINGER'S THEORY OF PERSONALITY

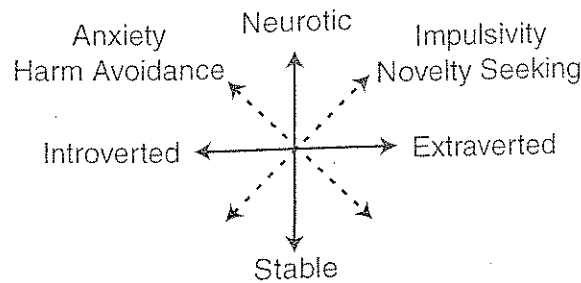
In contrast to Eysenck's three-factor model, Cloninger's (1994) revised biosocial model of personality posits seven domains of personality: four temperament domains ("harm avoidance," "novelty seeking," "reward dependence," and "persistence") and three character domains ("self-directedness," "cooperativeness," and "self-transcendence"). All seven of these domains are measured by the Temperament and Character Inventory (TCI; Cloninger, 1994), whereas the first three (harm avoidance, novelty seeking, and reward dependence) are measured by an earlier instrument, the Tridimensional Personality Questionnaire (TPQ; Cloninger, 1986). This section focuses on harm avoidance because, as will be shown, it also demonstrates a very strong phenotypic association with measures of mood and affect.

### Harm Avoidance

According to the model, harm avoidance is regulated by serotonergic cell bodies and reflects variation in the brain's "punishment system" or "behavioral inhibition system," which includes the septo-hippocampal system as well as serotonergic and cholinergic projections (Cloninger, 1987). Individuals high on harm avoidance are characterized as cautious, tense, apprehensive, fearful, inhibited, shy, easily fatigable, and worrying (Cloninger, 1994).

## THE OVERLAP AMONG GRAY, EYSENCK, AND CLONINGER

Gray (1986) argued that his dimensions of "anxiety" and "impulsivity" are not necessarily at odds with Eysenck's model of personality, and that his dimensions are at an approximate 45° rotation from Eysenck's dimensions of neuroticism and extraversion (Eysenck & Eysenck, 1985; Gray, 1970). This is illustrated in Figure 11.2, where "anxiety/harm avoidance" runs diagonally across the two-dimensional plane defined by "extraverted" and "neurotic," such that individuals with high harm avoidance fall within the neurotic/introverted quadrant.



**FIGURE 11.2.** Relationship between Eysenck's dimensions of neuroticism and introversion, Cloninger's harm avoidance and novelty seeking, and Gray's anxiety and impulsivity. From Eysenck and Eysenck (1985). Copyright 1985 by Eysenck and Eysenck. Adapted by permission.

Of course, the degree of overlap between the various dimensions of personality is an empirical question. Based on a sample of students, Zuckerman and Cloninger (1996) found that Harm Avoidance correlated highly with Neuroticism (0.59) and Extraversion ( $-0.53$ ). In the same study, the correlation was between EPQ Extraversion and Novelty Seeking (0.44). This was most likely attributable to the fact that the older version of Extraversion contained impulsivity items.

In a factor analysis of Cloninger's and Eysenck's dimensions, Heath, Cloninger, and Martin (1994) concluded that it would be erroneous to assume that they represent "alternative descriptions of the same dimensions of personality." Instead, they suggested that the TPQ and EPQ assess five to six discernible dimensions of genetic variability and at least six dimensions of environmental variability. Slutske and colleagues (1998), in a principal-components analysis of the TPQ and the Eysenck Personality Questionnaire—Revised (EPQ-R; Eysenck & Eysenck, 1991), extracted three higher-order personality dimensions. The first factor, labeled "positive emotionality," had high loadings of TPQ Reward Dependence and EPQ-R Extraversion. TPQ Harm Avoidance and EPQ-R Neuroticism loaded strongly onto the second factor, labeled "negative emotionality."

More recently, an analysis of data from the population-based Australian Twin Registry, using a sample of 3,269 twins ages 18–28 years, has yielded correlations of .58 to .60 for males and females, respectively, between EPQ-R Neuroticism and TPQ Harm Avoidance (Gillespie, Johnstone, Boyce, Heath, & Martin, 2001). High but negative correlations were also found between TPQ Harm Avoidance and EPQ-R Extraversion. These results suggest that harm avoidance does intersect Eysenck's neurotic-introverted quadrant. Indeed, in unpublished analyses using the same twin data, the genetic factors underpinning EPQ-R Neuroticism scores also explained significant proportions of variance in TPQ Harm Avoidance. This is demonstrated by the high additive genetic factor loadings in Table 11.3.

TABLE 11.3. Additive Genetic Factor Loadings Based on a Cholesky Triangular Decomposition of the EPQ-R (Neuroticism, Extraversion, Psychoticism, and Lie) and TPQ (Harm Avoidance, Novelty Seeking, and Reward Dependence) Personality Subscales

	Males (~1250)							Females (~2100)						
	1.	2.	3.	4.	5.	6.	7.	1.	2.	3.	4.	5.	6.	7.
1. Neuroticism	.64							.57						
2. Extraversion	-.20	.67						-.24	.63					
3. Psychoticism	.16	.18	.54					—	.19	.69				
4. Lie	—	-.22	—	.63				—	-.13	-.19	.56			
5. Harm Avoidance	.44	-.36	—	—	.34			.37	-.32	-.15	—	.29		
6. Novelty Seeking	—	.56	.27	-.18	—	-.17		—	.33	.26	-.26	—	.29	
7. Reward Dependence	-.14	.39	-.22	.16	—	—	.32	—	.30	-.23	—	—	—	.47

Note. Nonsignificant loadings are not shown. Data from Gillespie and colleagues (2001).

## PREDICTING PSYCHOLOGICAL DISTRESS

Having argued that there is a strong phenotypic association between neuroticism and related constructs such as harm avoidance, the next step is to demonstrate that the same personality dimensions are useful for predicting psychological distress. A chief advantage of the continuous dimensions of personality proposed by Eysenck, Gray, and Cloninger is that they provide a theoretical framework for explaining the biological and social mechanisms of anxiety and mood disorders, as well as a source of testable predictions.

Personality has long been thought to predispose individuals to mood and anxiety disorders (Eysenck, 1953; Eysenck & Rachman, 1965). Eysenck's model predicts that neurotic/introverted individuals, or what he referred to as "dysthymic personalities," are more prone to mood and mood disorders because they condition faster to neurotic responses. In terms of Figure 11.2, individuals who fall within the neurotic/introverted quadrant are more prone to experiencing anxiety, reactive depression, obsessions, phobias, and so on. There are good empirical data to support this prediction. Depressed subjects typically record higher EPQ or EPQ-R Neuroticism and Introversion scores (Corah, 1971; Eysenck, 1971a; Eysenck & Eysenck, 1985; Eysenck & Rachman, 1965; Larsen & Ketelaar, 1991; Maier, Lichtermann, Minges, & Heun, 1992). Other studies have demonstrated a strong phenotypic association between neuroticism and both clinical and symptomatic measures of depression (Berlanga, Heinze, Torres, Apiquian, & Caballero, 1999; Gormley, O'Leary, & Costello, 1999; Hassanyeh, Eccleston, & Davison, 1981; Kerr, Schapira, Roth, & Garside, 1970). The most recent evidence



comes from Middeldorp and colleagues, who present their results in Chapter 12 of this volume. They provide compelling evidence, based on data from the population-based Netherlands Twin Register, that there is a significant linear trend linking high neuroticism, low extraversion, and the number of mood and anxiety disorders.

Similarly, harm avoidance is a very good predictor of mood and anxiety disorders and symptoms: premenstrual depression (Freeman, Schweizer, & Rickels, 1995); self-reported depression (Hansenne, Pitchot, Gonzalez Moreno, Machurot, & Ansseau, 1998; Nelson, Cloninger, Przybeck, & Csernansky, 1996; Strakowski, Dunayevich, Keck, & McElroy, 1995; Strakowski, Faedda, Tohen, Goodwin, & Stoll, 1992; Yoshino, Kato, Takeuchi, Ono, & Kitamura, 1994); panic disorder associated with agoraphobia (Saviotti et al., 1991); DSM-III-R Cluster C personality disorders (Ampollini, Marchesi, Signifredi, & Maggini, 1997; Battaglia, Przybeck, Bellodi, & Cloninger, 1996), and other mood and anxiety disorders (Ampollini et al., 1997; Starcevic, Uhlenhuth, Fallon, & Pathak, 1996).

Strong phenotypic associations have been found among extraversion, neuroticism, and symptoms of anxiety (Bachorowski & Newman, 1990; Gershuny & Sher, 1998). Cox, Borger, Taylor, Fuentes, and Ross (1999), in a regression analysis of higher- and lower-order dimensions of the "Big Five" personality dimensions (see Costa & McCrae, 1992) based on 317 undergraduate students, found that higher-order domains of neuroticism and extraversion, as well as the lower-order neuroticism facets of anxiety and self-consciousness, best predict anxiety sensitivity.

### What Is the Nature of the Association?

Not only do people with various clinical forms of major depression consistently report higher levels of neuroticism (Fanous, Gardner, Prescott, Cancro, & Kendler, 2002; Kendler, Gardner, & Prescott, 2002; Kendler, Kessler, Neale, Heath, & Eaves, 1993; Kendler, Neale, Kessler, Heath, & Eaves, 1993b; Roberts & Kendler, 1999; Treloar, Martin, Bucholz, Madden, & Heath, 1999), but the association appears to be causal, because neuroticism or neuroticism-like traits can predict future cases of mood and anxiety disorders. Kendler and colleagues (1993b), in a study of 1733 same-sex female twin pairs, found that neuroticism was strongly related to lifetime prevalence of major depression. Neuroticism also predicted the prospective 1-year prevalence of major depression in those who, at time 1, denied previous depressive episodes, and this was not merely because of overlap with prodromal symptoms of major depression.

More evidence for a causal association comes from Kirk and colleagues (2000). As shown in Table 11.4, they found that high scorers on EPQ Neuroticism (Eysenck & Eysenck, 1975; S. B. G. Eysenck, Eysenck, & Barrett, 1985) when compared to low scorers, had significantly higher rates of DSM-IV diag-

TABLE 11.4. Prevalences (%) of DSM-IV Diagnoses for a Sample of Female and Male Twins Selected on the Basis of Extreme EPQ Neuroticism Scores (Obtained on Average 10 Years Prior to Formal Diagnoses)

DSM-IV diagnosis	Females				Males			
	Deciles		OR	<i>p</i>	Deciles		OR	<i>p</i>
	1 & 2 ( <i>n</i> = 852)	9 & 10 ( <i>n</i> = 676)			1 & 2 ( <i>n</i> = 495)	9 & 10 ( <i>n</i> = 447)		
Depression	14.0	41.1	2.9	***	10.9	32.7	3.0	***
Dysthymia	0.2	1.9	9.5	***	0.0	0.4	—	.14
OCD	1.4	9.2	6.4	***	1.6	11.0	6.9	***
Social phobia	2.1	11.4	5.4	***	1.6	12.5	7.8	***
GAD	1.0	1.6	1.5	.33	0.0	1.8	—	**
Panic w/o agoraphobia	1.3	4.1	3.2	***	0.4	2.9	7.2	**
Panic + agoraphobia	0.5	2.4	4.8	***	0.0	2.7	—	**
Agoraphobia w/o panic	0.7	4.1	5.9	***	0.0	1.3	3.2	.12

Note. OR, odds ratio. Data from Kirk et al. (2000).

\**p* < .05; \*\**p* < .01; \*\*\**p* < .001.

noses of major depression, dysthymia, obsessive-compulsive disorder (OCD), panic disorder with or without agoraphobia, agoraphobia without panic disorder, social phobia, and GAD. Most interestingly, selection was based on the 12-item short-scale Neuroticism questionnaire given, on average, 10 years prior to the formal DSM-IV diagnoses' being made.

## THE GENETIC EPIDEMIOLOGY OF PSYCHOLOGICAL DISTRESS AND PERSONALITY

The next step is to explain this relationship more precisely in terms of genetic and environmental effects. The branch of science referred to as "behavior genetics" is distinct from fields such as sociobiology or evolutionary psychology, because it focuses on the role of genetic and environmental influences as contributors to individual differences. The chief advantage of this approach is that it permits researchers to generate and test explicit hypotheses regarding the genetic and environmental etiology of complex behaviors.

### Genetic Epidemiology of Major Depression

Evidence for the genetic contribution to major depression is compelling and comes from a variety of study designs, many of which rely on large population-based twin registries (Bierut et al., 1999; Kendler, Gardner, & Prescott, 1998; Kendler, Heath, Martin, & Eaves, 1986, 1987; Kendler, Karkowski, Corey, & Neale, 1998; Kendler, Neale, Kessler, Heath, & Eaves,

1992a, 1993a; Kendler, Pedersen, Neale, & Mathe, 1995; Kendler & Prescott, 1999; Kendler et al., 1994; Lyons et al., 1998; McGuffin, Katz, Watkins, & Rutherford, 1996; Silberg et al., 1999; Tambs, 1991). A significant genetic component is consistently found, regardless of whether the analyses are based on self-report or continuous symptom counts (Kendler et al., 1986, 1987, 1994; Tambs, 1991), on clinical categorical diagnoses (Bierut et al., 1999; Kendler et al., 1992a; Kendler, Pedersen, et al., 1995; Kendler & Prescott, 1999; Kendler, Walters, et al., 1995; Lyons et al., 1998; McGuffin et al., 1996; Silberg et al., 1999), or hospital or clinical samples (Kendler, Pedersen, Johnson, Neale, & Mathe, 1993; Kendler, Pedersen, et al., 1995; McGuffin et al., 1996).

In the same way that lifetime prevalence estimates change as a function of varying definition, the estimates of environmental and genetic variance underpinning variation in major depression also vary. Table 11.2 also includes standardized genetic and environmental variance components under the best-fitting models for twin pair resemblance, as a function of the particular diagnostic systems. For all nine definitions, there was no evidence to support the contribution of shared environmental or cultural effects in the etiology of major depression. Instead, family aggregation (i.e., the degree to which siblings and genetically related family members are more or less alike) could be entirely explained by significant but moderate proportions of additive genetic variance. With the exception of the WUC, which exclude secondary cases, the magnitude of genetic influence appears to be similar regardless of whether depression is broadly or narrowly defined. In other words, for seven of the definitions, the genetic contribution to major depression ranged from 33% to 45%, whereas for the two definitions that were restricted to only primary cases of major depression, the genetic contribution was much lower (from 21% to 24%).

Despite the inherent limitations of meta-analysis, the least of which is the heterogeneity of samples (see Eysenck, 1994a, 1995), Sullivan, Neale, and Kendler (2000) have reviewed the literature that has explored the sources of familial aggregation for major depression. In their meta-analysis, six twin studies met the authors' inclusion criteria, which included more than 21,000 subjects who had received the DSM-III-R interview for major depression (Bierut et al., 1999; Kendler, Pedersen, et al., 1995; Kendler & Prescott, 1999; Lyons et al., 1998; McGuffin et al., 1996).

Equating the response thresholds for opposite-sex dizygotic twin pairs provided a poor fit to the data, which is indicative of significant sex differences in the prevalence previously mentioned. Yet, despite significant sex difference in prevalence, the estimates of genetic and environmental variance across sex as well as between clinical and nonclinical samples could be equated. In terms of the liability to major depression, the best-fitting model estimated that additive genetic effects explained 37% of the variance in major depression, while the remaining variance was explained entirely by aspects of the environment that were unshared between siblings. Again, there was no

evidence of cultural or shared environmental effects. In other words, there is nothing to suggest that variation in vulnerability to major depression is environmentally transmitted from parents to offspring or influenced by common environmental factors shared within families. Rather, the most salient features of the environment are aspects that are unique to twins, and a proportion of this variance must also include measurement error.

### Genetic Epidemiology of Anxiety Disorders

Evidence for a genetic contribution to anxiety disorders is equally compelling and also comes from a variety of study designs (Chantarujikapong et al., 2001; Hettema, Prescott, & Kendler, 2001; Hudson et al., 2003; Kendler, Neale, Kessler, Heath, & Eaves, 1992b, 1992c; Kendler, Walters, et al., 1995; Koenen et al., 2002; Mendlewicz, Papadimitriou, & Wilmotte, 1993; Noyes, Clarkson, Crowe, Yates, & McChesney, 1987; Scherrer et al., 2000; Skre, Onstad, Torgersen, Lygren, & Kringlen, 1993; Sullivan, Kovalenko, York, Prescott, & Kendler, 2003; Torgersen, 1983).

Hettema, Neale, and Kendler (2001) meta-analyzed data from family and twin studies of panic disorder, GAD, phobias, and OCD. Their results based on the twin studies are summarized in Table 11.5. Three twin studies

TABLE 11.5. Summary of Population-Based Twin Studies that Have Investigated the Genetic (A) and Environmental (C/E) Etiology of Anxiety Disorders

Diagnosis	Sex	Components of variance		
		A	C	E
DSM-III-R GAD	Male	.32	—	.68
DSM-III-R GAD	Female	.32	.17	.51
DSM-III-R panic disorder <sup>a</sup>	Female	.37	—	.63
DSM-III-R panic disorder <sup>a</sup>	Male	.43	—	.57
DSM-III social phobia	Female	.30	—	.70
DSM-III agoraphobia	Female	.39	—	.61
DSM-III simple phobia, animal	Female	.32	—	.68
DSM-III simple phobia, situational	Female	—	.27	.73
DSM-III simple phobia, medical	Female	—	.32	.68
DSM-III social phobia	Male	.20	—	.80
DSM-III agoraphobia	Male	.37	—	.63
DSM-III simple phobia, animal	Male	.35	—	.65
DSM-III simple phobia, situational	Male	.25	—	.75
DSM-III simple phobia, medical	Male	.28	—	.72

*Note.* A, C, and E, proportions of variance attributable to additive genetic, shared environmental, and nonshared environmental effects, respectively. Best-fitting final models only are shown. From Hettema, Neale, and Kendler (2001). Copyright 2001 by the American Psychiatric Association. Adapted by permission.

that included almost 13,000 subjects (Hettema, Prescott, & Kendler, 2001; Scherrer et al., 2000; Skre et al., 1993) met the author's inclusion criteria, but only two of them provided estimates of genetic and environmental heritability. Data from the two larger studies by Scherrer and colleagues ( $n = 6724$ ) and Hettema and colleagues ( $n = 6200$ ) were combined; the GAD definition of 1 month's minimum duration was used. The best-fitting model for GAD estimated that 32% (95% confidence interval = 24–39%) of the variance in GAD was best explained by additive genetic effects, and that the same genes predisposed men and women alike to GAD.

There were important sex differences, and unlike the genetics of major depression, there was evidence that shared environmental or cultural effects contributed to 17% of the variation in male GAD. This was also in contrast to the two twin studies examining panic disorder. Meta-analysis of results based on the two community samples revealed that the model parameters could be combined across sex. Under the best-fitting models, additive genetic effects explained 43% of the variance, while the remaining variance was entirely attributable to aspects of the environment that were unshared between siblings.

## Genetic Epidemiology of Personality

Evidence for the genetic contributions to individual differences in adult personality comes from studies of twin pairs reared together (Eaves & Young, 1981; Loehlin & Nichols, 1976; Rose & Kaprio, 1988; Rose, Kaprio, Williams, Viken, & Obremski, 1990; Rose, Koskenvuo, Kaprio, Sarna, & Langinvainio, 1988); separated twin pairs (Bouchard, Lykken, McGue, Segal, & Tellegen, 1990; Pedersen, Plomin, McClearn, & Friberg, 1988; Shields, 1962; Tellegen et al., 1988); nontwin adoptees and their biological and adoptive families (Loehlin, 1982, 1985; Loehlin, Horn, & Willerman, 1981; Scarr, Webber, Weinberg, & Wittig, 1981); and twin pairs reared together and their relatives—parents, siblings, spouses, and adult children (Eaves, 1978; Eaves, Heath, Neale, Hewitt, & Martin, 1998; Lake, Eaves, Maes, Heath, & Martin, 1999; Price, Vandenberg, Iyer, & Williams, 1982). Although a variety of assessment instruments have been used in different studies, a core of Extraversion and Neuroticism items from the Eysenck personality questionnaires (the Maudsley Medical Questionnaire, Maudsley Personality Inventory, Eysenck Personality Inventory, EPQ, and EPQ-R), or equivalent items, have been used in most studies.

Among the numerous reports based on twin data that have examined the heritability of neuroticism and extraversion, nearly all have arrived at genetic estimates in the vicinity of 50% (Eaves & Eysenck, 1975; Eaves et al., 1998, 1999; Fanous et al., 2002; Floderus-Myrhed, Pedersen, & Rasmuson, 1980; Heath et al., 1997; Jang, Livesley, & Vernon, 1996; Jardine, Martin, & Henderson, 1984; Jinks & Fulker, 1970; Kendler, Neale, Kessler, Heath, & Eaves, 1993; Macaskill, Hopper, White, & Hill, 1994; Martin, Eaves, & Fulker, 1979; Pedersen et al., 1988; Rose et al., 1988; Saudino,

Pedersen, Lichtenstein, McClearn, & Plomin, 1997; Viken, Rose, Kaprio, & Koskenvuo, 1994).

More recently, population-based twin studies have begun exploring the genetic epidemiology of other personality dimensions, such as Cloninger's (1994) dimensions of temperament and character, and the five-factor model of personality proposed by Costa and McCrae (1992). Familial aggregation for Cloninger's dimension of harm avoidance, which is closely related to Eysenck's neuroticism, can be almost entirely explained by genetic effects (Cloninger et al., 1998; Heath et al., 1994; Page & Martin, 1998). Despite theoretical debate over the relationship or overlap between Eysenck's dimension of psychoticism and Costa and McCrae's dimensions of openness, agreeableness, and conscientiousness, the two dimensions of extraversion and neuroticism in the Big Five are closely related to the same dimensions in the Eysenckian model (Costa & McCrae, 1995).

### **Sources of Covariance among Neuroticism, Mood Disorders, and Anxiety Disorders**

The phenotypic association between measures of psychological distress and personality, including the evidence for significant heritability in each, raises the question of whether the observed correlations reflect common genetic or environmental diatheses, or whether there are genetic or environmental effects that are unique to each phenotype and condition.

Based on data from the Australian Twin Registry, Jardine and colleagues (1984) examined the covariance between the symptoms of anxiety and depression, using a shortened version of the Delusion Symptoms States Inventory (Bedford & Deary, 1997; Foulds & Bedford, 1975) as well as the Neuroticism scale from the EPQ (Eysenck & Eysenck, 1975). Their results revealed that the phenotypic covariation between the two measures could be best explained by a single genetic factor common to both measures. There was no evidence for genetic factors specific to one measure and having no influence on the other. In a longitudinal design based on 1733 same-sex female twin pairs, Kendler and colleagues (1993b) have estimated that the proportion in the observed correlation between neuroticism and the liability to major depression that could be explained by a shared genetic risk was approximately 70%. In the same study, extraversion was unrelated to lifetime or 1-year prevalence of major depression.

Using the same data from the study by Jardine and colleagues (1984), Kendler and colleagues (1986) showed that the covariation between the symptoms of anxiety and depression is influenced by the same genes, but that the syndromes are differentiated by unique environment stressors. Although the covariance appears to best be explained by a single underlying continuum of liability, Neale and Kendler (1995) have tested a number of alternative but more complex models that could also explain the association between major depression and GAD. These include (1) random multiformity, in which affec-

tive status on one disorder abruptly increases risk for the second; (2) extreme multiformity, where only extreme cases have an abruptly increased risk for the second disorder; (3) three independent disorders, in which excess comorbid cases are due to a separate, third disorder; (4) correlated liabilities, where the risk factors for the two disorders correlate; and (5) direct causality, where the liability for one disorder is a cause of the other disorder. When based on a large population-based sample of 2,163 female twins, their results were unfortunately equivocal, with several models providing comparable fits to the data. Less equivocal, however, was the conclusion that comorbidity is best represented by two correlated liability distributions, and that a model of alternative forms of a single dimension of liability provides a better fit when compared to a model of three independent disorders (i.e., major depression, GAD, and major depression with GAD).

Bivariate analyses based on adolescent populations have also supported Kendler and colleagues' (1986) "same genes, different environment" hypothesis (Eley, 1999; Eley & Stevenson, 1999a, 1999b). These findings have also been replicated when based on DSM-III and DSM-III-R diagnoses of major depression and GAD (Kendler, 1996; Kendler et al., 1992c, 1993b; Kendler, Walters, et al., 1995), and altering the diagnostic criteria does not change the overall picture. The genetic covariance between major depression and GAD is consistent, regardless of whether or not the diagnostic hierarchies for GAD include mood or psychotic disorders, or whether the minimum duration of illness is reduced from 6 months to 1 month (Kendler et al., 1992c).

## CONCLUSIONS

Identification of the genes predisposing individuals to anxiety disorders and depression would be a major breakthrough in psychiatric genetics and would reset the research agenda both in academic psychiatry and in the pharmaceutical industry. The first step in this process is conducting replicated linkage studies to provide a firm foundation for fine mapping and gene identification. Ultimately, we hope that this work will lead to a more comprehensive understanding of mood and anxiety disorders, and at the same time improve the treatment of some of society's most burdensome diseases.

## LOOKING FORWARD

Despite the knowledge that heredity plays an important role in personality, mood, and anxiety, locating the quantitative trait loci for these complex traits and for disorders linked to them has proved difficult, although there have been some successes—for example, Crohn's disease (Low et al., 2004; Peltekova et al., 2004; Stoll et al., 2004), schizophrenia (Berrettini, 2004; O'Donovan, Williams, & Owen, 2003; Riley, 2004), and asthma (Cookson,

2002; Cookson & Moffatt, 2002; Halapi & Hakonarson, 2004; Wills-Karp & Ewart, 2004).

Among a number of genes, those controlling serotonin (5-HT) remain strong candidates. Owens and Nemeroff (1994), in their review, have shown considerable evidence to support the hypothesis that there are significant differences in the serotonergic systems of patients with and without major depression. Based on Lesch and colleagues' (1996) finding that the short allele of the serotonin transporter gene (*5-HTTLPR*) reduces the transcriptional efficiency, Caspi and colleagues (2003) have since reported that variation in this polymorphism moderates the influence of stressful life events on major depression. However, replication has proven difficult (see Gillespie, Whitfield, Williams, Heath, & Martin, 2005). In terms of personality, Sen, Burmeister, and Ghosh (2004) have reported a highly significant association between *5-HTTLPR* and NEO Personality Inventory Neuroticism, but they found no association with TCI/TPQ Harm Avoidance or with any other anxiety-related personality traits, and EPQ Neuroticism was not included in the analyses. Lesch and Canli (Chapter 13, this volume) show how individual differences in anxiety-related personality traits correlate with genetic variations in the *5-HTTLPR* pathway, specifically with a functional C-1019G single-nucleotide polymorphism in the transcriptional control region of the 5-HT<sub>1A</sub> receptor gene.

Genome-wide linkage analyses of neuroticism with anxiety and depression in England (Fullerton et al., 2003), Iceland (Thorgeirsson et al., 2003), and the United States (Abkevich et al., 2003; Holmans et al., 2004; Zubenko et al., 2003) are beginning to yield converging results. These studies also highlight the need for replication before fine mapping can begin. Other studies using the "extremely discordant and concordant" sibling pairs design are underway in Australia (Kirk et al., 2000), the Netherlands (Boomsma et al., 2000), and England (Sham et al., 2000), and results will soon be appearing. If the examples of schizophrenia and bipolar disorder are guides (see Levinson, Levinson, Segurado, & Lewis, 2003; Lewis et al., 2003; Segurado et al., 2003), truth will emerge not from any one study, but from careful meta-analysis of a large number of these very large studies.

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