

GENETIC AND OTHER VULNERABILITY FACTORS FOR ANXIETY AND STRESS DISORDERS

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Despite dramatic advances in our understanding of genetics and neurobiology, the etiology of the anxiety disorders is still relatively unknown. To date, there remain no pathogenomic markers with which a presumptive diagnosis of an anxiety disorder may be made. This highlights the importance of the empirical epidemiologic approach to investigating the definitions and risk factors for the expression of anxiety across the life course. Anxiety disorders are developmental conditions that often emerge during childhood and follow varied developmental trajectories (1,2). Research on early-life vulnerability factors that predict the trajectory of anxiety symptoms across development holds promise for elucidating mechanistic pathways in anxiety.

In evaluating the risk factors for the development of anxiety disorders, there are several issues requiring consideration. First, there is substantial overlap between the anxiety disorders and other psychiatric disorders both concomitantly and longitudinally. Second, manifestations of anxiety change substantially across the life course, particularly during childhood and adolescence. Therefore, a developmental perspective is essential in evaluating links between risk factors and anxiety disorders. Third, the assessment of anxiety requires evaluation of the context in which the individual experiences anxiety as well as the subjective response to anxiety-inducing situations. As such, anxiety becomes a disorder when there is a mismatch between inherent threat posed by a particular stimulus or situation and the cognitive or somatic response.

Research on vulnerability factors has undergone a relatively marked transformation in recent years, due to conceptual changes in causal theories of mental disorders. Such conceptual changes are reflected in three major themes that organize current research on vulnerability factors in anxiety.

First, although studies through the early 1990s often emphasized the role of one or another particular risk factor, more recent studies emphasize the manner in which multiple risk factors might interact to cause mental syndromes, including anxiety, as part of a mechanistic pathway. For example, although dysregulation in fear conditioning has been linked to anxiety for more than two decades (3), such dysregulation is now viewed as part of a larger chain of intrinsic and extrinsic events that may ultimately culminate in an anxiety disorder (4). Second, as a corollary to this view, vulnerability markers are now conceptualized as tied to families of anxiety disorders, as opposed to specific conditions. This change in perspective follows the observation that validators of individual mental syndromes related to differential course, familial aggregation, or psychophysiology relate more closely to families of disorders than to particular disorders. Third, marked advances over the past 20 years in neuroscience have stimulated a closer integration of basic and clinical work on vulnerability markers in anxiety disorders. Progress in elucidating neural circuits related to anxiety has facilitated research on vulnerability markers for anxiety disorders that integrates data from basic and clinical science.

This chapter examines the major risk factors for the development of anxiety disorders across the life span. Particular attention is paid to the specificity of vulnerability factors and to developmental differences in expression of the disorders themselves.

MAGNITUDE AND DEMOGRAPHIC RISK FACTORS

Magnitude of Anxiety in General Population

The anxiety disorders are the most common psychiatric disorders both in the United States and elsewhere (2,5,6). The

results of the two large-scale community-based surveys of psychiatric disorders of adults in the United States, the Epidemiological Catchment Area study (ECA) (2) and the National Comorbidity Study (NCS) (5), reveal that the total prevalence rates of anxiety disorders are greater than those of the affective disorders, behavior disorders, and substance use disorders. Phobias tend to be the most common anxiety disorder, whereas panic disorder is fairly rare in the general population. There is substantial overlap both cross-sectionally and longitudinally between the anxiety disorders and other disorders, as well as between the subtypes of anxiety disorders themselves (6). On average, there is a threefold increased risk of having a second disorder compared to that of manifesting an anxiety disorder alone across the lifetime.

Comorbidity between anxiety disorders and other psychiatric disorders has been demonstrated in both clinical and community samples. Anxiety disorders are most strongly associated with affective disorders and with substance use disorders (6), though they are generally associated with all other major classes of disorders including depression, disruptive behaviors, eating disorders, and substance use. Comorbidity between anxiety disorders and other disorders in the *Diagnostic and Statistical Manual of Mental Disorders*, third edition revised or fourth edition (DSM-III-R or -IV) may be even more common in adolescents than in adults (7). A review of comorbidity of anxiety and depression by Brady and Kendall (8) suggests that anxiety and depression may be part of a developmental sequence in which anxiety is expressed earlier in life than depression. Although the association between anxiety and depression is quite consistent, the evidence of links between anxiety disorders and behavior problems is inconclusive.

Sex Differences in Anxiety Disorders

Similar to the affective disorders, females tend to exhibit greater rates of anxiety disorders, though there is some vari-

ability according to specific subtypes. Table 61.1 presents the sex-specific lifetime rates of the major subtypes of anxiety disorders assessed in the ECA and NCS (5,6). Although the magnitude of the rates of anxiety disorders varies substantially between the two studies, the sex ratio is strikingly similar: women have an approximately twofold elevation in lifetime rates of panic, generalized anxiety disorder, agoraphobia, and simple phobia than men in both studies. In contrast, there is a nearly equal sex ratio for the lifetime prevalence of social phobia.

There is increasing evidence from community-based studies that anxiety symptoms and disorders are also the most common problems in childhood and adolescence as well. The rates of anxiety disorders in community or school-based surveys of children and adolescents as defined by contemporary diagnostic criteria range from 0.1% to 13.3% in males and 0.4% to 28.6% in females (9). Similar to the sex ratio for adults, girls tend to have more of all subtypes of anxiety disorders, irrespective of the age composition of the sample. For example, in a recent epidemiologic study, females compared to males had greater rates of current anxiety disorders (i.e., 12.2% vs. 8.5%), past anxiety disorders (5.2% vs. 2.7%), as well as anxiety symptom scores on a dimensional rating (mean = 1.9 vs. 0.9) (10). Nevertheless, Lewinsohn et al. (10) reported that despite the greater rates of anxiety in girls across all ages, there was no difference between boys and girls in the average age at onset of anxiety (mean for girls = 8.0 ± 3.9 ; mean for boys = 8.5 ± 3.8).

Age-Specific Patterns of Expression of Anxiety Disorders

Retrospective reports of adults with anxiety disorders suggest that the onset of anxiety disorders generally occurs in childhood or adolescence. Although there is substantial

TABLE 61.1. SEX-SPECIFIC LIFETIME PREVALENCE RATES OF ANXIETY DISORDERS IN COMMUNITY SURVEYS IN THE UNITED STATES

	Epidemiologic Catchment Area Study (5)			National Comorbidity Survey (6)		
	Males	Females	Sex Ratio (F:M)	Males	Females	Sex Ratio (F:M)
Anxiety disorders						
Anxiety disorders, total	1.8	10.3	5.7	19.2	30.5	1.6
Generalized anxiety disorder	4.3	6.8	1.6	3.6	6.6	1.8
Panic disorder	0.9	2.0	2.2	2.0	5.0	2.5
Phobic disorders						
Agoraphobia without panic	3.2	7.9	2.5	3.5	7.0	2.0
Simple phobia	7.8	14.5	1.9	6.7	15.7	2.3
Social phobia	2.5	2.9	1.2	11.1	15.5	1.4

variation across studies, the results of prospective community-based research reveal differential peak periods of onset of specific subtypes of anxiety: separation anxiety and specific phobias in middle childhood (i.e., ages 7 to 9); overanxious disorder in late childhood (i.e., 10 to 13); social phobia in middle adolescence (i.e., 15 to 16); and panic attacks, sometimes progressing to panic disorder, in late adolescence (i.e., 17 to 18) (1,11–14). Anxiety disorders, particularly the phobias, tend to persist across the life course. However, there are major differences among the anxiety subtypes in terms of specificity and chronicity. Whereas the phobic states tend to be fairly stable and nonprogressive, generalized anxiety and panic tend to be less specific and less stable over time (1,15,16).

Several follow-up studies of children and adolescents have shown that anxiety symptoms and disorders in general tend to exhibit some stability, but with substantial switching across categories of anxiety disorders over time (17,18). A recent 8-year follow-up study of a community sample of youth ages 9 to 18 at study entry provides compelling evidence of the stability of the subtypes of anxiety disorders (17). The stability of both social phobia and simple phobia was highly specific over time, whereas overanxious disorder was associated with major depression, social phobia, and generalized anxiety in early adulthood.

Epidemiologic surveys of adults reveal that the female preponderance of anxiety disorders is present across all stages of life but is most pronounced throughout early and mid-adulthood. The rates of anxiety disorders in males are also rather constant throughout adult life, whereas the rates in females peak in the fourth and fifth decades of life and decrease thereafter. The increased rates in females are present across all ages and do not diminish as the rates of anxiety decrease in late life. The importance of pure anxiety disorders in late life was described by Beekman et al. (19), who found different risk factors for anxiety disorders than for either depression or comorbid anxiety and depression in a community sample of adults over age 55.

Social Class and Ethnicity

Rates of anxiety disorders in general are greater among those at lower levels of socioeconomic status (20). Several community studies have yielded greater rates of anxiety disorders, particularly phobic disorders, among African-Americans (5). With respect to children, Compton et al. (14) found that Caucasian children were more likely to report symptoms of social phobia, whereas African-American children had more separation anxiety symptoms. Pine et al. (1) reported that phobias were greater among those at lower levels of social class. The reasons for ethnic and social class differences have not yet been evaluated systematically; however, both methodologic factors as well as differences in exposure to stressors have been advanced as possible explanations.

FAMILIAL AND GENETIC FACTORS

The familial aggregation of all of the major subtypes of anxiety disorders has been well established (21). As reviewed below, the results of more than a dozen controlled family studies of probands with specific subtypes of anxiety disorders converge in demonstrating a 3- to 5-fold increased risk of anxiety disorders among first-degree relatives of affected probands compared to controls. The importance of the role of genetic factors in the familial clustering of anxiety has been demonstrated by numerous twin studies of anxiety symptoms and disorders (22,23). However, the relatively moderate magnitude of heritability also strongly implicates environmental etiologic factors. Table 61.2 summarizes the results of family and twin studies of anxiety disorders.

Review of Family and Twin Studies of Anxiety Disorders in Adults

Panic Disorder

Of the subtypes of anxiety, panic disorder is the anxiety syndrome that has been shown to have the strongest degree of familial aggregation. A recent review of family studies of

TABLE 61.2. SUMMARY OF FAMILY AND TWIN STUDIES OF ANXIETY DISORDERS

Type of Study	Comparison	Number of Studies	Average Relative Risk	Range
Family	Rel of probands vs. rel of controls	13 panic	5.4	(4.2–17.8)
		4 social phobia	3.1	(2.5–9.7)
		3 general anxiety	4.3	(2.7–5.6)
		3 OCD	3.5	(1.0–5.1)
Twin	MZ vs. DZ	3 panic	2.4	(2.2–2.5)
		4 phobias	2.6	(1.4–9.5)
		1 OCD	4.9	—

DZ, dizygotic; MZ, monozygotic; OCD, obsessive-compulsive disorder.

panic disorder by Gorwood et al. (24) cited 13 studies that included 3,700 relatives of 780 probands with panic disorder compared to 3,400 relatives of 720 controls. The lifetime prevalence of panic was 10.7% among relatives of panic probands compared to 1.4% among relatives of controls, yielding a relative risk of 6.8. In addition, early-onset panic, panic associated with childhood separation anxiety, or panic associated with respiratory symptoms has each been shown to have a higher familial loading than other varieties of panic disorder (25).

Although there has been some inconsistency reported by twin studies of panic disorder (26), two studies applying modern diagnostic criteria demonstrated considerably higher rates for monozygotic compared to dizygotic twins (27,28). Furthermore, current estimates derived from the Virginia Twin Registry show panic disorder to have the highest heritability of all anxiety disorders at 44% (29).

Phobic Disorders

Though there are far fewer controlled family and twin studies of the other anxiety subtypes, all of the phobic states (i.e., specific phobia, agoraphobia) have also been shown to be familial (30–33; see refs 34–36 for reviews). The average relative risk of phobic disorders in the relatives of phobics is 3.1. Stein et al. (33) found that the familial aggregation of social phobia could be attributed to the generalized subtype of social phobia. Data from the Virginia Twin Study report the estimated total heritability for phobias to be 35% (29,37).

Generalized Anxiety Disorder

There is also evidence of both the familial aggregation and heritability of generalized anxiety disorder in a limited number of studies. The average familial odds ratio is approximately 5 (32,38), and the heritability was 0.32 among female twin pairs (37).

Obsessive-Compulsive Disorder

Likewise, there are also very few controlled family studies of obsessive-compulsive disorder. Two of the three studies (39,40) reported familial relative risks of 3 to 4, whereas Black et al. (41) found no evidence for familial aggregation. Nestadt et al. (40) found that both the age of onset and obsessions were associated with greater familiarity. Twin studies have yielded weak evidence for heritability of obsessive compulsive disorder (42–44).

Linkage and Association Studies

Based on indirect evidence implicating the adrenergic system in panic disorder (45), several linkage studies have investigated the role of mutations in adrenergic receptor loci

on chromosomes 4, 5, or 10 (46), but without success. Other work has similarly excluded linkage with γ -aminobutyric acid receptor A (GABA_A) genes (47). Reports from a genomic survey of panic disorder using 600 markers have not yielded evidence of linkage (48). Similarly, linkage studies have excluded the possibility that panic disorder was due to mutations in adrenergic receptor loci on chromosomes 4, 5, or 10 (46), and other work has similarly excluded linkage with GABA_A receptor genes (47). Recent reports from a genomic survey of panic disorder using 600 markers have not yielded evidence of linkage (48).

Family Studies and Phenotypic Definitions

The lack of success in identifying specific genes for anxiety disorders is not surprising given their complexity. Similar to several other psychiatric disorders, the anxiety disorders are complicated by etiologic and phenotypic heterogeneity, a lack of valid diagnostic thresholds, unclear boundaries between discrete anxiety subtypes, and comorbidity with other forms of psychopathology. Impediments to estimating genetic influences in youth are demonstrated by dramatic differences in heritability according to the informant regarding child psychopathology. For example, Eaves et al. (49) found that the heritability of both separation anxiety and overanxious disorder was far greater for parent-reported rather than child-reported disorder.

The family study approach, particularly when employed with systematic community-based samples, is one of the most powerful strategies to minimize heterogeneity because etiologic factors for the development of a particular disorder can be assumed to be relatively homotypic within families. There is a dearth of studies that have employed within-family designs to examine either phenotypic expression or some of the putative biological factors underlying the major anxiety disorders. For example, both Perna et al. (50,51) and Coryell (52) have shown that healthy relatives of probands with panic disorder have increased sensitivity to CO₂ challenge, suggesting that CO₂ sensitivity may be a promising trait marker for the development of panic, as described below. Smoller and Tsuang (36) discuss the value of family and twin studies in identifying phenotypes for genetic studies.

Both family and twin studies have been used to examine sources of overlap within the anxiety disorders, and between the anxiety disorders and other syndromes including depression, eating disorders, and substance abuse. Fyer et al. (31, 53) have demonstrated the independence of familial aggregation of panic and phobias. With respect to comorbidity, whereas panic disorder, generalized anxiety, and depression have been shown to share common familial and genetic liability (23,54,55), there is substantial evidence for the independent etiology of anxiety disorders and substance use disorders (36,55,56). Similar results have emerged from

studies of symptoms of anxiety and depression in youth in which both anxiety and depression was found to result from common genetic diathesis (57,58).

In a comprehensive consideration of what may be inherited, Marks (59) reviews the components of anxiety that have been investigated in both human and animal studies. Evidence from twin studies has indicated that somatic manifestations of anxiety may lie under some degree of genetic control. These studies demonstrate that physiologic responses, such as pulse, respiration rate, and galvanic skin response, are more alike in monozygotic than in dizygotic twin pairs. Furthermore, twin studies of personality factors have shown high heritability of anxiety reaction. Finally, the results of animal studies have suggested that anxiety or emotionality is under genetic control. Selective breeding experiments with mammals have demonstrated that emotional activity analogous to anxiety is controlled by multiple genes (59). These findings suggest that anxiety and fear states are highly heterogeneous and that future studies need to investigate the extent to which the components of anxiety result from common versus unique genetic factors and the role of environmental factors, either biologic or social, in either potentiating or suppressing their expression.

High-Risk Studies of Anxiety Disorders

Given the early age of onset for anxiety disorders, studies of children of parents with anxiety have become an increasingly important source of information on the premorbid risk factors and early forms of expression of anxiety. Increased rates of anxiety symptoms and disorders among offspring of parents with anxiety disorders have been demon-

strated by Turner et al. (60), Biederman et al. (61), Sylvester et al. (62), Last et al. (63), Warner et al. (64), Beidel and Turner (65), Beidel (66), Capps et al. (67), Merikangas et al. (68), Unnewehr et al. (69), and Warner et al. (70). Table 61.3 presents the risk of anxiety disorders among offspring of parents with anxiety disorders compared to controls averages 3.5 (range 1.3 to 13.3), suggesting specificity of parent-child concordance within broad subtypes of anxiety disorders.

However, similar to studies of adults that show common familial and genetic risk factors for anxiety and depression (27,71,72), studies in children have also revealed a lack of specificity with respect to depression (60,64,65,73). Studies that employed a comparison group of parent probands with depressive disorders have shown that rates of anxiety disorders are also increased among the offspring of these parents (60,62,65,70); conversely, offspring of parents with anxiety disorders and depression have elevated rates of depression when compared to those of controls (62) or to offspring of anxiety-disordered parents without depression (61). Similar findings emerged from the family study by Last et al. (63), who found an increase in rates of major depression among the adult relatives of children with anxiety. Weissman et al. (74) have even suggested that childhood anxiety represents one of the earliest manifestations of familial risk for depression. These findings are usually interpreted as providing evidence for age-specific expression of common risk factors for anxiety in childhood and depression with or without comorbid anxiety in adulthood.

The high rates of anxiety disorders among offspring of parents with anxiety suggest that there may be underlying psychological or biological vulnerability factors for anxiety disorders in general, which may already manifest in children

TABLE 61.3. CONTROLLED HIGH-RISK STUDIES OF ANXIETY

Study	Sample					Offspring		Relative Risk
	Proband		Other	Spouse	N	Age		
	Anxiety	Other						
Sylvester et al., 1987 (73)	Panic	MDD	—	No Dx	91	7–17	13.3	
Turner et al., 1987 (60)	Agoraphobia/OCD	Dysthymia	—	Not evaluated	43	7–12	4.8	
Capps et al., 1996 (67)	Agoraphobia	Agoraphobia/Panic	—	Not evaluated	43	8–24	—	
Warner et al., 1995 (64)	Panic/MDD	Panic	Early-onset MDD	Dx	145	6–29	1.3	
Beidel et al., 1997 (65)	Anxiety + depression	Anxiety	MDD	No Dx	129	7–12	4.0	
Merikangas et al., 1998 (68)	Panic/social phobia	Alcohol or drugs	Substance + anxiety	Dx	192	7–17	2.0	
Unnewehr et al., 1998 (69)	Panic	Simple	—	Not evaluated	87	5–15	9.2	

Dx, diagnosis; MDD, major depressive disorder.

prior to puberty. Previous research has shown that children at risk for anxiety disorders throughout life are characterized by behavioral inhibition (75), autonomic reactivity (66,76), somatic symptoms (60,77), social fears (60,62), enhanced startle reflex (76), and respiratory sensitivity (160). Empirical research on each of these domains of risk is reviewed in the next section.

VULNERABILITY MARKERS

The current section reviews recent studies on vulnerability markers in anxiety disorders. This includes data on temperamental factors and biological profiles. The first section reviews evidence regarding individual-level vulnerability factors, whereas the subsequent section examines data linking exogenous or environmental factors with risk for anxiety. As noted above, both sets of vulnerability markers operate within complex causal chains involving multiple interacting risk factors. Moreover, in such complex chains, the boundary between intrinsic and exogenous risk factors can become blurred. For example, the effects of exogenous factors, including life events; social rearing experiences, such as trauma or parental nurturance; and factors such as the use of illicit substances may operate through effects on intrinsic factors, such as the regulation of neural systems that monitor danger.

Intrinsic, individual-oriented vulnerability markers for anxiety disorders can be conceived across a range of perspectives, focusing on increasingly more specified biological systems. At the most complex or global level, specific temperamental or personality characteristics, such as neuroticism, harm avoidance, and behavioral inhibition have been linked to risk for anxiety. At a more specified level, vulnerability can be modeled through the assessment of cognitive function, in the form of attention and memory, or peripheral physiologic function, as reflected in autonomic reactivity profiles, changes in the startle reflex, or changes in ventilatory control. These cognitive and physiologic functions, in turn, reflect functional aspects of neurochemical or neuroanatomic systems that are presumably homologous with systems linked to fear and anxiety across a range of mammalian species. Data from humans at each of these levels is reviewed within the context of research on fear and anxiety in other species.

Temperament/Personality

Behavioral Inhibition

One of the earliest indicators of vulnerability to the development of anxiety is behavioral inhibition, characterized by increased physiologic reactivity or behavioral withdrawal in the face of novel stimuli or challenging situations (79). Behavioral inhibition may be a manifestation of a biological

predisposition characterized by both overt behavioral (e.g., cessation of play, latency to interact in the presence of unfamiliar objects and people) and physiologic indicators (e.g., low heart rate variability, accelerated heart rate, increased salivary cortisol level, pupillary dilation, increased cortisol level). There is an increased frequency of behavioral inhibition among children of parents with anxiety disorders compared to those of normal controls (61,62,65,75,80–82).

Few studies have evaluated the differences in manifest inhibition and approach/avoidance in both clinical and nonclinical samples, leaving gaps in the conceptualization of the construct of inhibition. Some studies have shown that there is more stability of behavioral inhibition across early childhood among girls than among boys (83). The expression of behavioral inhibition studied prospectively may reveal patterns of anxiety symptomatology similar to those endorsed in adult populations. In a prospective study of a large community cohort of subjects from age 3 months to 13 years, Prior et al. (84) found that maternal ratings of persistent shyness and shyness in late childhood were associated with the development of anxiety disorders in adolescence.

Anxiety Sensitivity

Anxiety sensitivity is another potential sensitive and specific trait marker for the development of anxiety disorders (85). Anxiety sensitivity is characterized by beliefs that anxiety sensations are indicative of harmful physiologic, psychological, or social consequences (e.g., fainting or an impending heart attack). The misinterpretation of bodily cues that characterizes anxiety sensitivity may lead to a self-perpetuating “fear of fear” cycle. Thus, the fear of benign arousal sensations produces anxiety, which in turn increases the frequency and intensity of physiologic sensations, and subsequently fuels apprehension regarding the significance of these sensations. This process may ultimately result in a full-blown panic attack.

Anxiety sensitivity is thought to represent a stable trait-like factor that is qualitatively different from general fear and anxiety (86). It has been proposed that anxiety sensitivity may interact with environmental experiences (e.g., hearing misinformation about the negative outcome of certain bodily sensations) to shape beliefs about the dangers of anxiety sensations. Thus, anxiety sensitivity may be involved in the development of certain anxiety disorders, particularly panic disorder (87,88). Of particular interest is the finding of the specificity of anxiety sensitivity with respect to development of anxiety disorders but not depression in a nonclinical sample (88). Likewise, Pollock et al. (89) reported that anxiety sensitivity appears to be specific to anxiety, as it did not contribute unique variance above self-rated anxiety symptoms in the prediction of depressive symptoms.

Anxiety sensitivity has been shown to be under genetic (90) and familial influence; anxiety sensitivity was found to

constitute a potential premorbid marker for the development of anxiety disorders in high-risk but not low-risk youth (89). Prospective studies of youth have also demonstrated the prognostic significance of anxiety sensitivity in predicting the development of anxiety disorders. Based on the results of a 5-year prospective study of adolescents, Hayward et al. (91) concluded that anxiety sensitivity appeared to be a specific risk factor for the development of panic attacks in adolescents. These findings from prospective research, particularly the specificity with respect to anxiety, together with the importance of genetic and familial liability suggest that anxiety sensitivity is an important vulnerability factor that should be examined in future studies.

Comorbid Disorders

Psychiatric

The magnitude of comorbidity in adults and adolescents with anxiety suggests that investigation of the role of other disorders in enhancing the risk of the initial development and persistence of anxiety disorders over time may be fruitful. The difficulty in dating onset of specific disorders, particularly from retrospective data, diminishes our ability to determine the temporal relations between disorders. Nevertheless, some prospective studies have examined the links between anxiety disorders and earlier expression of other forms of psychopathology. For example, whereas some studies suggest that childhood depression may presage the onset of panic attacks, the results of a fairly large prospective study suggest a bilateral temporal association between panic attacks and depression (91).

Other disorders that may enhance the risk of development of anxiety disorders include eating disorders (92), depression, and substance use and abuse. With respect to substance use disorders, Rao et al. (93) found that anxiety disorders may comprise a mediator of the link between depression and the subsequent development of substance use disorders in a clinical sample. The potential mechanisms through which anxiety may be associated with smoking in adolescents were examined by Patton et al. (94), who found that both anxiety and depression were associated with smoking initiation through increased susceptibility to peer influences. Conversely, some research suggests that substance use may trigger anxiety disorders in susceptible youth. For example, a prospective study of a community sample revealed that posttraumatic stress disorder (PTSD) may be triggered by substance abuse in about 50% of the cases (95). Similarly, Johnson et al. (96) found that adolescent smoking predicted adult onset of panic attacks, panic disorder, and agoraphobia (96). Thus, although comorbidity between anxiety and both depression and substance problems is quite common in children and adolescents, further research on the mechanisms for links between specific disorders both across and within genders is necessary.

Medical Symptoms/Disorders

Several studies have also suggested that there is an association between childhood medical conditions and the subsequent development of anxiety. Kagan et al. (97) reported an association between allergic symptoms, particularly hay fever, and inhibited temperament in young children. In a retrospective review of pre- and perinatal and early childhood risk factors for different forms of psychiatric disorders in adolescence and early adulthood, Allen et al. (98) found that anxiety disorders in adolescents were associated specifically with illness during the first year of life, particularly high fever. Likewise, Allen and Matthews (102) reported that adolescents and young adults with anxiety disorders were more likely to have suffered from infections during early childhood than others. The prevalence of high fevers in childhood along with other diseases associated with immune system were also elevated among offspring of parents with anxiety disorders in the Yale High Risk Study (76). Kagan (101) proposed that the high levels of cortisol associated with anxiety may lead to immunologic sensitivity to environmental stimuli. Taylor et al. (99) reported that immunologic diseases and infections were specifically associated with emotional disorders because children with developmental or behavioral disorders had no elevation in infections or allergic diseases. On the other hand, Cohen et al. (100) suggest that such medical problems show stronger associations with depressive as opposed to anxiety disorders during adolescence. These findings suggest that it may be fruitful to examine links between immunologic function and the development of anxiety disorders.

Prospective studies have revealed that the anxiety disorders may comprise risk factors for the development of some cardiovascular and neurologic diseases. Haines et al. (103) reported that phobic anxiety was associated with ischemic heart disease, particularly fatal ischemic events. Bovasso and Eaton (104) employed cardiac and respiratory symptoms and illness to subtype panic attacks and their association with depression in a large community-based sample. They found that “respiratory panic attacks were associated with the subsequent risk of myocardial infarction.” Likewise, phobic disorder is strongly associated with migraine, with the onset of phobias predating that of migraine (105,106). The results of both family studies and prospective cohort studies suggest that there may be a subtype of migraine with shared liability for anxiety and depression (105).

Autonomic Reactivity

Reactions to threatening stimuli among various organisms, including primates and lower mammals, involve changes in the autonomic nervous system. These changes can be detected through an analysis of time series for heart rate, heart period variability, blood pressure, and catecholamine levels.

There is a long history of research in this area, and much of the initial work concerned the assessment of physiologic changes associated with acute anxiety states. Hence, acute episodes of anxiety, both in the laboratory and in natural settings, are typically characterized by acute changes in heart rate, blood pressure, and heart period variability (107). These changes result from coordinated changes in the parasympathetic and sympathetic innervation of the cardiovascular system.

More recent work on physiologic changes during acute anxiety states has attempted to identify specific physiologic patterns associated with one or another emotion. The identification of such emotion-specific patterns may provide insights on emotion-specific patterns of brain activity. For example, some forms of anxiety, such as acute panic, may be characterized by marked parasympathetic withdrawal in the face of sympathetic enhancement. Other emotions, such as anger, may be characterized by a distinct physiologic “finger print,” reflecting the involvement of distinct brain systems across emotions (108–110). In general, consistent associations are found across development between acute anxiety states and changes in peripheral autonomic indices, including heart rate, blood pressure, or heart period variability. As a result, some suggest that perturbations in autonomic regulation may index an underlying vulnerability to develop anxiety disorders. This underlying vulnerability is thought to relate to the functioning of particular neural circuits within the brain that exert effects on both subjective internal states and physiologic activity. Potentially relevant neural circuits have been identified through basic science studies on the neural basis of fear and anxiety.

Despite consistent evidence of an association between acute anxiety states and changes in autonomic physiology, the degree to which such changes index vulnerability for anxiety, as opposed to the acute state of anxiety, remains unclear. If such changes in autonomic physiology primarily reflect downstream manifestations of relatively high degrees of acute fear, they would provide limited advantages as vulnerability markers. On the other hand, at least some of the underlying autonomic abnormalities in panic disorder persist after remission and may be independent of the current state. This suggests that changes in autonomic physiology may mirror subtle person-specific differences in brain processes related to the processing of risk or to the experience of fear. As such, autonomic indices might index vulnerability in a fashion that is more sensitive than indices derived through self-report measures. A series of recent studies provide preliminary evidence consistent with this possibility.

Autonomic physiologic profiles have been studied among individuals who face high risk for anxiety disorders. Physiologic profiles have been tied to at least three indicators of risk: temperamental factors, family history, and traumatic events. In terms of temperamental factors, Kagan (111)

noted the relationship between behavioral inhibition, which predicts later anxiety, and a distinct autonomic physiology profile. Children with behavioral inhibition exhibit an autonomic physiology characteristic of the profile found during acute anxiety. Specifically, behaviorally inhibited children exhibit under conditions of novelty a shift from parasympathetic to sympathetic control of the cardiovascular system, manifest as an increase in heart rate and a reduction in high-frequency components of the heart period variability power spectrum. Such abnormalities in autonomic physiology are viewed as downstream reflections of perturbations based within the limbic system. In terms of family history, Bellodi et al. (112) found similar temperamental and physiologic abnormalities among children of parents with panic disorder. Such data are consistent with other studies finding high rates of behavioral inhibition among offspring of patients with anxiety disorders. Finally, in terms of traumatic events, physiologic reactions to an acute stress may index underlying vulnerability to develop anxiety states. Consistent with this possibility, Shalev et al. (113) found that enhanced cardiovascular activity in the emergency room immediately following a motor vehicle accident predicted the development of PTSD.

Taken together, available data clearly delineate associations between acute anxiety and autonomic physiology profiles, but the implications of this work for the study of risk remain unclear. Moreover, the underlying assumption in this work posits an effect of perturbations in brain systems on both autonomic physiology and anxiety symptoms. As such, more work is also needed relating brain function to autonomic physiology.

Psychophysiological Function

Research on fear conditioning has facilitated an integration of basic and clinical work on vulnerability for anxiety. Fear conditioning develops following the pairing of a neutral “conditioned” stimulus (CS+), such as a tone or a light, and an aversive “unconditioned” stimulus (UCS), such as a shock, a loud noise, or an air puff. Across a range of mammalian species, including humans, fear conditioning results from changes in a relatively simple neural circuit that involves distinct amygdala nuclei, including the basolateral and central nucleus. Basic science research on the role of this circuit in learned fears has also called attention to the role played by related but relatively distinct neural circuits in the responses to other forms of danger. For example, reactions to intrinsically dangerous contexts, such as a brightly lit room for a rodent, involve a relatively extended period of vigilance. These reactions may more intimately involve the basolateral nucleus and the bed nucleus of the stria terminalis than the central nucleus of the amygdala. Such reactions in animals may model worry in humans as characteristically found in many anxiety disorders (114).

Similarly, acute reactions to intrinsically dangerous stimuli often involve rapid changes in behavior designed to facilitate escape or defense. Such reactions in animals may involve the hypothalamus and lower brainstem structures; such reactions in animals may be model acute panic in humans.

Work in neuroscience delineating circuits involved in mammal's response to danger has stimulated a series of studies on risk for anxiety in humans. Much of this work quantifies physiologic reactions to innate and learned fears with the goal of comparing physiology across high- and low-anxiety groups. Based on skin conductance data, Eysenck and Eysenck (115) suggested that abnormal habituation of conditioned fear responses confers risk for anxiety. Similarly, Raine et al. (116) suggest that deficiencies in learned fear, as modeled by skin conductance, relates to low anxiety and high risk for chronic behavior problems. However, due to methodologic advantages, more recent studies rely on startle as a physiologic index of activity in brain circuits tied to fear. Most importantly, it has been possible to map circuits that regulate startle in more precise detail, relative to circuits that regulate skin conductance or other indicators of autonomic response, such as heart rate. Cross-species parallels in startle regulation facilitate integration of basic and clinical work (76,114,117–124). For example, molecular genetic studies on fear conditioning in mice generate specific hypotheses on the genetics of risk human disorders (125–131). Fear-relevant stimuli in animals may potentiate startle through effects on genes in limbic structures, such as the amygdala, that are involved in fear conditioning. In adult humans, distinct stimuli effect startle across emotional disorders, but abnormal startle in some form is seen in many disorders, including phobias (132), PTSD (122–124), depression (133,134), and panic disorder (135). Moreover, there is some evidence that startle specifically indexes risk for anxiety. Three studies found startle abnormalities in children born to adults with an array of anxiety disorders (76,119), and a fourth study found startle abnormalities in inhibited children, who face high risk for anxiety disorders (111).

In a high-risk study of offspring of parents with anxiety disorders compared to psychiatric and normal controls, the startle reflex and its potentiation by aversive states was used as a possible vulnerability marker to anxiety disorders in adolescent offspring of parents with anxiety disorders (122). Startle was found to discriminate between children at high- and low-risk for anxiety disorders, as well as to discriminate between children at risk for anxiety compared to those at risk for alcoholism. However, different abnormalities in startle amplitude for high-risk males and females were observed. Startle levels were elevated among high-risk females, whereas high-risk males exhibited greater magnitude of startle potentiation during aversive anticipation. Two possible explanations for the gender differences in the high-risk groups were suggested by the authors: (a) differential sensitivity among males and females to explicit threat versus the

broader contextual stimuli that are mediated by different neurobiologic pathways, and (b) different developmental levels in males and females in which the vulnerability to anxiety may be physiologically expressed earlier in females.

Nevertheless, more work in this area is needed, given inconsistencies across genders and across conditions under which startle is most discriminatory (76). These data are also consistent with the findings of Watson et al. (136). Overall, the data suggest that startle indices may provide an important window for assessing dysfunction in limbic circuits broadly related to mood and anxiety regulation.

Ventilatory Function

As in the area of autonomic physiology, a wealth of research delineates associations between respiratory perturbation and acute anxiety. This association has been most convincingly demonstrated in panic disorder, where various forms of respiratory stimulation, including lactate infusion (137) and CO₂ inhalation, consistently produce high degrees of anxiety and more pronounced perturbations in respiratory physiologic parameters. Of note, these associations extend beyond the specific diagnosis of panic disorder, because enhanced sensitivity to respiratory perturbation is also found in conditions that exhibit strong familial or phenomenologic associations with panic disorder, including limited symptom panic attacks; certain forms of situational phobias; childhood anxiety disorders, particularly separation anxiety disorder; and high ratings on anxiety sensitivity scales.

Compared to the work on autonomic physiology, a larger body of research implicates abnormalities in respiration in risk or vulnerability for anxiety. At least four sets of findings suggest that respiratory indices index risk for anxiety, independent of any association between current state and respiratory function. First, asymptomatic adult relatives of patients with panic disorder consistently exhibit enhanced subjective sensitivity to respiratory stimulation, in the form of exogenously inhaled CO₂ (51,138,139). Second, among patients with panic disorder, stronger family loading is found in panic patients with evidence of respiratory dysregulation, as opposed to those with no sign of respiratory dysregulation (51,140). Third, respiratory indices linked to panic disorder are strongly heritable, raising questions on the potential shared genetic vulnerability for panic attacks and respiratory dysregulation. Fourth, Pine et al. (78) reported increased carbon dioxide sensitivity in children with anxiety disorders. Such data are also consistent with work on respiratory disease (141) and smoking (96,142), which suggest that abnormalities in respiration predispose to later anxiety. Based on this work, abnormalities in respiration appear to provide some information on the vulnerability for anxiety states that are related to acute panic.

Despite the consistency of findings in this area, a number of questions remain. The most consistent data emerge for

subjective indices of respiratory sensitivity, manifest as a tendency to report dyspnea during stress or during respiratory stimulation. The mechanisms that contribute to such enhanced sensitivity remain poorly specified. At a cognitive level, such hypersensitivity may result from an overall sensitivity to somatic sensations, consistent with data linking high degrees of anxiety sensitivity to future panic attacks (143). On the other hand, enhanced sensitivity to respiratory sensations appears more closely tied to panic attacks than sensitivity to other somatic factors; the tie between anxiety sensitivity and respiratory sensitivity also appears relatively weak in some studies. At the physiologic level, such hypersensitivity may result from perturbations in brain systems involved in respiratory regulation or primary as opposed to learned fear states. Unfortunately, the precise role of fear systems in both respiratory regulation and human anxiety states also remains poorly specified.

Neurochemical and Neurohormonal Factors

As reviewed in other sections of this book, extensive data document associations between alterations in various neurochemical factors and ongoing anxiety disorders. This includes data on the serotonergic, noradrenergic, and GABAergic systems. Moreover, there is some evidence to implicate neurochemical alterations in the causal chain contributing to anxiety disorders. In animal models, genetic manipulations of serotonergic receptors, the serotonin reuptake transporter gene, and components of the GABA complex each produce behavioral and physiologic effects reminiscent of clinical anxiety states. Similarly, clinical studies find that acute pharmacologic manipulations in these neurochemical systems produce concomitant change in acute anxiety. For example, the inverse GABA agonist flumazenil precipitates anxiety in patients with panic disorder, whereas GABA agonists are potent treatments for various forms of anxiety. These findings are consistent with evidence of a deficiency in GABAergic modulation among adults with anxiety disorders. Similarly, manipulations of the serotonergic system, either through tryptophan depletion or treatment with medications, also produce both acute and more chronic changes in anxiety. Finally, manipulations of the noradrenergic system produce similar changes in both children and adults. Sallee et al. (144) found that the α_2 -agonist yohimbine elevated selectively anxiety symptoms and was associated with blunting of growth hormone in children with anxiety disorders. Interestingly, as with the response of children to CO₂ inhalation (160), the response to yohimbine appeared particularly abnormal in children with separation anxiety disorder. However, evidence of perturbed noradrenergic function in children with depression or facing high familial risk for depression (145) suggest that these findings may not be specific to anxiety but rather may relate to broad risk for mood and anxiety disorders.

Despite the consistency of these findings relating neurochemical factors to anxiety, relatively few studies have examined the manner in which individual differences in neurochemical function predict vulnerability to anxiety. There is evidence from studies in adult patients that some of these neurochemical abnormalities persist after remission. For example, much like symptomatic patients, remitted patients with panic disorder exhibit abnormal secretory profiles in terms of the growth hormone and the hypothalamic-pituitary-adrenal (HPA) axis. These neurohormonal abnormalities are thought to reflect trait-related abnormalities in neurochemical systems involved in neurohormonal regulation. Finally, there have been numerous studies of patients and at-risk relatives using lactate challenge to induce anxiety (146–148). The limited information provided on neural pathways by this provocation test limits its value in informing the pathophysiology of anxiety disorders.

Although these studies raise the possibility that risk for anxiety may result at least partially from underlying neurochemical abnormalities, other studies are needed to confirm this possibility. For example, there are almost no studies of neurochemical function in high-risk youth, a key source of information regarding the underlying role of biological parameters in the development of anxiety disorders. One exception is the study of Reichler et al. (77), who assessed several biological factors in their high-risk study of panic disorder including lactate metabolism, mitral valve prolapse, urinary catecholamines, and monoamine oxidase. Although none of these parameters discriminated high-risk from low-risk youth, the lack of differences may have been attributable in part to low statistical power.

Likewise, very few studies have compared neurochemical function in asymptomatic relatives of patients with and without anxiety disorders. Similarly, no studies have examined family loading for anxiety disorders in patients stratified in terms of their neurochemical functioning.

Beyond this work examining monoamine systems' influence on neurohormonal regulation and vulnerability for anxiety, a relatively extensive body of work examines the precise relationship between anxiety and HPA axis regulation. Corticotropin-releasing factor (CRF) represents a key neuropeptide in the regulation of this system. CRF infusions in animals produce behavioral and physiologic effects in animals that bear similarities to human anxiety states. Similarly, genetic manipulations that alter CRF produce similar effects. As such, this work suggests that an underlying dysregulation in the HPA axis, possibly centrally involving CRF, may contribute to vulnerability for anxiety. Consistent with basic science studies, clinical research notes a relationship between acute anxiety states and alterations in HPA axis function. For example, a variety of acute stressors induce consistent elevations of cortisol; patients with PTSD exhibit multiple signs of HPA axis dysregulation; multiple

other anxiety disorders exhibit other signs of HPA axis dysregulation.

Vigilance/Attention

Studies of the association between attention regulation and anxiety have revealed that adults with anxiety disorders exhibit enhanced vigilance for threat cues, as indexed by effects of fear-related words or pictures on reaction times. These effects have been attributed to amygdala influences on attention allocation (149–153). Enhanced attentional bias in acute anxiety represents a particularly robust finding, noted in more than 20 studies using various paradigms across virtually all anxiety disorders. These effects appear particularly robust in two paradigms, the emotional Stroop and the dot-probe tests. From a theoretical perspective, this enhanced bias is considered a vulnerability marker that antedates the developmental of anxiety disorders among adults. Consistent with this possibility, an enhanced bias for threat cues is found early in the course of anxiety disorders, particularly among children with anxiety disorders. On the other hand, this enhanced bias is generally not found in remitted patients (153), and studies have yet to document enhanced bias for threat cues in at-risk but asymptomatic individuals.

ENVIRONMENTAL EXPOSURES

Perinatal Exposures

There is virtually no evidence that either prenatal factors or delivery complications comprise risk factors for the development of anxiety disorders. The results of three studies that retrospectively assessed perinatal events converged in linking such exposures to behavioral outcomes, but not to subsequent anxiety. For example, Allen et al. (98) found that children who suffered from a variety of exposures ranging from prenatal substance use to postnatal injuries were more likely to develop behavior disorders, particularly attention deficit disorder and conduct problems, but not anxiety disorders. Likewise, the results of the Yale High-Risk Study yielded no association between pre- and perinatal risk factors and the subsequent development of anxiety disorders (76).

Life Events/Stressors

The role of life experiences in the etiology of anxiety states, particularly phobias and panic disorder, has been widely studied (154–157). Life events have often been designated a causal role in the onset of phobias, which are linked inherently to particular events or objects. More broadly, life experiences that to some extent threaten one's notion of safety and security in the world are often at least retrospectively perceived to trigger or precipitate the onset of anxiety disorders.

In evaluating the evidence on the causal role of life experiences, it is critical to consider separately the subtypes of anxiety disorders. Although it is likely that life stress may exacerbate phobic and generalized anxiety states, Marks (59) concludes that phobic states resulting from exposure are far more rare than those that emerge with no apparent exposure. In contrast, posttraumatic stress disorder (PTSD) is defined as a sequela of a catastrophic life event.

The major impediment to evaluation of the causal role of life events in anxiety (or depression) is the retrospective nature of most research addressing this issue. For example, Lteif and Mavissakalian (158) found that patients with panic or agoraphobia exhibited an increased tendency to report life events in general; this suggests that studies that limit assessment of life events to those preceding onset of a disorder may be misleading because they fail to provide comparison for the time period of onset. Moreover, stressful life events may interact with other risk factors such as family history of depression in precipitating episodes of panic (159). In one of the few prospective studies, Pine et al. (160) did demonstrate a predictive relationship between life events during adolescence and both depressive as well as generalized anxiety disorder symptoms. Interestingly, the association with anxiety was limited to females, consistent with differential vulnerability to stress across genders.

In terms of specific environmental risk factors, there has been abundant literature on the role of parenting in enhancing vulnerability to anxiety disorders. Based on Bowlby's (161) theory that anxiety is a response to disruption in the mother-child relationship, it has been postulated that maternal overprotection is related to anxiety, particularly separation anxiety. Using the Parental Bonding Instrument of Parker et al. (162), several studies of clinical samples have found that adult patients with anxiety disorders recall their parents as less caring and more overprotective than did controls (163). These findings have been supported in nonclinical samples as well (164,165). However, all of these studies caution that a causal link cannot be established because of the lack of independent assessment of parent behaviors and offspring anxiety.

Another parental behavior that may enhance risk of anxiety in offspring is parental sensitization of anxiety through enhancing cognitive awareness of the child to specific events and situations such as bodily functions, social disapproval, the importance of routines, and necessity for personal safety (164). Bennet and Stirling (164) found that subjects with anxiety disorders and those with high trait anxiety reported greater maternal and paternal overprotection and increased maternal sensitization to anxiety stimuli than controls.

Another feature of the parental relationship that has received widespread attention in recent research has been exposure to severe childhood trauma through either separation or abuse (161,166). There is increasing animal research on the impact of early adverse experiences on brain systems and subsequent development (167,168). Pynoos et al. (169)

present a comprehensive developmental life-trajectory model for evaluating the effects of childhood traumatic stress and anxiety disorders. They propose different avenues by which dangerous circumstances, childhood traumatic experiences, and PTSD can intersect with other anxiety disorders across the life span. The developmental perspective is critical in light of different levels of neural response to experience at different stages of development (170).

SUMMARY AND FUTURE DIRECTIONS FOR RESEARCH ON ANXIETY VULNERABILITY

Despite the rich array of constructs associated with anxiety (Table 61.4), our ability to predict those who will suffer from anxiety disorders in adulthood is severely limited. The principles of multifinality (i.e., many outcomes of the same risk factor) and equifinality (i.e., diverse risk profiles leading to the same endpoint) apply to many of the risk pathways investigated herein (171). Although we distinguish between intrinsic and extrinsic risk factors for the development of anxiety disorders, there is increasing evidence that there is a bidirectional association between the factors subsumed under these two domains. Only a small proportion of those with known vulnerability factors truly develop anxiety disorders in adulthood, despite the vast majority of those with adulthood anxiety reporting onset in childhood and early adolescence.

The major impediments to identifying specific risk factors for anxiety are exclusive reliance on retrospective data, blurred boundaries between normal and pathologic anxiety, difficulty distinguishing between risk factors and early manifestations of anxiety, limited interdisciplinary conceptualization of models of risk and pathogenesis, lack of evidence

of the specificity of risk factors with respect to anxiety disorders or subtypes thereof, and limited tools for direct measurement of brain function. Moreover, many of the risk factors have been shown to operate differently according to gender and age, as well as the specific subtype of anxiety. Elucidation of the different risk profiles will provide valuable information on classification, etiology, treatment, and prevention.

Future research should do the following:

- Establish more accurate and developmentally sensitive methods of assessment of anxiety, with a focus on developing objective measures of the components of anxiety.
- Apply within-family design to minimize etiologic heterogeneity and to refine diagnostic boundaries and thresholds.
- Investigate specificity of putative markers with respect to other psychiatric disorders and the longitudinal stability of specific subtypes of anxiety disorders.
- Develop research on hormonally mediated neurobiological function in order to understand gender differences predisposing women to experience decreased resiliency to fear-provoking stimuli.
- Examine mechanisms for associations between panic attacks with extrinsic exposures (i.e., substance use), developmental periods (i.e. pubertal development), and cessation in later life.

ACKNOWLEDGMENTS

This work was supported primarily by grant DA05348 and in part by grants AA07080, AA09978, DA09055, MH36197, Research Scientist Development Awards K02 DA00293 (to Dr. Merikangas), from Alcohol, Drug Abuse, and the Mental Health Administration of the United States Public Health Service.

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TABLE 61.4. VULNERABILITY FACTORS FOR ANXIETY DISORDERS

Individual
Genetic factors
Temperament
Behavioral inhibition
Anxiety sensitivity
Preexisting psychiatric/Medical disorder
Autonomic reactivity
Respiratory sensitivity
Neurobiological factors
Neuroendocrine factors
Exogenous
Exposure to stress
Drug use
Parenting
Modeling
Sensitization
Life events

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