39 Anxiety Disorders

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The current chapter reviews five anxiety disorders: phobic disorders, separation anxiety disorder, social anxiety disorder, generalized anxiety disorder and panic disorder. It is organized around four themes. The first section focuses on diagnosis, nosology and assessment. The second summarizes data on prevalence, risk factors and outcome. The third reviews research on family genetics and psychobiology. Treatment is summarized in the final section.

Clinical Presentation of Childhood Anxiety Disorders

Diagnosis

For phenomena that fall on a continuum, extremes have been viewed alternatively as severe expressions of continuously distributed traits or as distinct pathological entities. Controversy remains regarding the relative advantages and disadvantages in conceptualizing pediatric anxiety as a continuous or categorical phenomenon. A key reason for categorizing children presenting in the clinic as affected by anxiety disorders is to allocate services for those anxious children most in need. However, categorization of one or another group of child does not imply distinct etiology.

Distinguishing normal anxiety from pathological anxiety can be problematic because childhood anxieties are not only common, but may be adaptive. Diagnostically, anxiety may be considered pathological at any age if it limits developmentally appropriate behavior and thus causes functional limitation. However, anxiety may be considered pathological even when the child's activities are not affected but there is significant distress. Classification of children with little or no manifest impairment and only distress is often difficult, because the threshold for considering distress as clinically significant varies according many factors, such as the child's age, life circumstances or cultural background. Another guide for diagnosis is the child's ability to recover from anxiety. As such, failure to adapt represents a hallmark of pathology.

Disagreements on definitional boundaries between normal and pathological anxiety are likely to persist as long as clinical descriptors remain the exclusive basis for diagnosis. Other data may shed light, leading to nosological changes by identifying which syndromes carry long-term significance. As with definitions of hypertension, the definition of "abnormal" anxiety could change as longitudinal data identify factors that contribute to excessive long-term risk (Pine, Cohen, Gurley *et al.*, 1998; Pine, Cohen, & Brook, 2001). Eventually, advances in genetics or neuroscience also may impact nosology. However, considerable progress is needed before such approaches can provide clinical utility.

Nosology of Childhood Anxiety Disorders

Delimitating specific syndromes that facilitate communication among professionals is not a trivial accomplishment, but it represents a minimal standard for a useful nomenclature. While DSM-IV and ICD-10 meet this minimal goal, questions concerning the distinctiveness of anxiety disorders persist. These questions emerge as a result of comorbidity among anxiety disorders, coupled with inconsistent findings of distinct natural histories and factors used to validate diagnosis. The ICD-10 and DSM-IV have similar diagnoses for childhood anxiety disorders. The major difference concerns the handling of comorbidity: ICD-10 provides a single diagnosis for co-occurring anxiety and behavior disorders, whereas the DSM-IV requires separate diagnoses for each condition. In addition, obsessive compulsive disorder (OCD) and post-traumatic stress disorder (PTSD) are classified as anxiety disorders in the DSM-IV, but not in ICD-10 (these are not considered in this chapter because they are clinically distinct from the disorders examined here). Finally, some differences exist in the definitions of childhood anxiety disorders between ICD-10 and DSM-IV (Klein, 1994); however, this chapter focuses on common clinical features.

Presentation of Specific Anxiety Disorders

Phobic Disorder

Phobic disorder is defined by marked unreasonable fear of a specific object that is not intrinsically dangerous, such as animals, or a situation, such as heights. The level of fear is considered extreme, and exposure invariably elicits extreme fear. In addition, the phobia must either cause clinically significant distress or impair the person's well-being by leading to interference with ordinary activities because of avoidance. Phobic disorders may begin at any age, but typical onset is in childhood (Fyer, 1998; Pine *et al.*, 1998). Phobias can be

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classified based on the nature of the feared object: animals, natural environments, blood infection; or specific situations, such as elevators. Most children with phobic disorders share a limited number of feared situations. Attempts to differentiate among phobias on pathophysiological grounds have not yielded divergent features, except for blood injury phobia (Fyer, 1998), whose distinct physiological signature consists of a sudden drop in blood pressure, heart rate and fainting.

Separation Anxiety Disorder

Separation anxiety disorder represents the only anxiety diagnosis that must begin in childhood. In ICD-10, onset must be in early childhood, whereas in the DSM-IV, onset must occur any time before age 18. The onset is frequently in late childhood, before adolescence, and decreases as children mature into adolescence. As the name connotes, the disorder reflects anxiety at separation from home or caretakers that causes impairment by leading to avoidance. The terms "school phobia" and "school refusal" have been used to describe a pattern of school avoidance (Egger, Costello, & Angold, 2003). In preadolescents, refusal to attend school because of fears is most often related to separation anxiety disorder. Feared separations situations often seem illogical. For example, a child may have no difficulty going to school, but be highly anxious while visiting familiar friends' homes. Difficulty sleeping alone is especially salient in children with separation anxiety disorder. As reviewed below, some evidence suggests relationships between childhood separation anxiety disorder and adult panic disorder.

Social Phobia/Social Anxiety Disorder

Social anxiety disorder is characterized by anxiety in a range of social situations because of fear of scrutiny, ridicule, humiliation or embarrassment. Some children may not articulate these concerns but feel uncomfortable in social settings. Children must experience discomfort with peers, not only with adults, and anxiety cannot be caused by impaired capacity for socialization, as evidenced by the fact that the children interact satisfactorily with those who are familiar to them. The diagnostic distinction between severe social anxiety disorder and mild pervasive developmental disorder can be problematic. Chronic avoidance of social interactions might limit development of social competence, contributing to similarities with mild pervasive developmental disorder. However, in general, children and adolescents with social anxiety desire social contacts, whereas those with pervasive developmental disorder typically lack interest in reciprocal relationships.

The diagnostic qualifier, generalized social phobia, denotes anxiety in multiple social settings. There are no standard definitions for distinguishing it from the non-generalized form, leading to divergent interpretations. Some apply the non-generalized label to individuals who experience social anxiety in only one or two situations, such as parties; others use the diagnosis for individuals who experience only performance anxiety, such as public speaking, eating in front of people, as well as test anxiety, but who do not have anxiety during social interactions. Performance anxiety may occur without significant anxiety in social situations, but the reverse is unusual.

Epidemiological evidence supports the distinction between generalized and non-generalized social anxiety disorder. The generalized form has been reported to have earlier onsets, more chronicity, more comorbidity and more psychopathology in relatives (Wittchen, Stein, & Kessler, 1999). This work exemplifies how epidemiological studies can inform diagnostic validity.

Generalized Anxiety Disorder

Generalized anxiety disorder encompasses multiple worries about a variety of life circumstances, such as school work, one's appearance or future. The age of onset is poorly understood, but typically is not in early childhood. Prior to the DSM-IV, "overanxious disorder" was used for children and adolescents with multiple worries. It remains unclear to what degree the outdated diagnosis of overanxious disorder overlaps with generalized anxiety disorder (Pine *et al.*, 1998). Generalized anxiety disorder is the only anxiety disorder that requires somatic symptoms. However, there is no documentation that these occur preferentially in this anxiety disorder.

Relative to other anxiety disorders, generalized anxiety disorder has very high rates of comorbidity, and it rarely presents on its own in clinic patients. Beyond comorbidity with other anxiety disorders, it has a strong relationship with major depressive disorder (Costello *et al.*, 2002; Kessler *et al.*, 2002). This high comorbidity raises questions about whether the diagnosis identifies a unique syndrome as opposed to a complication of other associated disorders. Because the symptoms consist mostly of worries, the disorder is not usually characterized by avoidant behavior, although there are exceptions. For example, children with extreme worries about academic performance may miss school on testing days.

Panic Disorder

The essential clinical feature of panic disorder is the repeated experience of unprovoked spontaneous panic attacks, which may lead to limited independent travel or agoraphobia. The panic attacks are characterized by intense fear of impending doom, accompanied by physical symptoms, such as rapid heartbeat, shortness of breath, choking sensation, sweating, depersonalization or derealization. To some extent, these symptoms identify meaningful subtypes of panic disorder patients. Thus, patients who present with respiratory symptoms have been reported to differ from other panic disorder patients in treatment response and familial aggregation (Briggs, Stretch, & Brandon, 1993; Horwath, Adams, Wickramaratne, *et al.*, 1997). Usual onset begins with spontaneous panic attacks, typically during adolescence. Progression to full-blown panic disorder occurs in a minority, typically during early adulthood (Pine *et al.*, 1998).

Diagnostic confusion arises concerning panic disorder because panic reactions can occur in many anxiety states, including in various phobias during exposure to feared situations. The key distinction is that, in panic disorder, panic attacks

occur without cues, as prototypically exemplified by nocturnal panic attacks. Moreover, young children may display panic reactions, but whether they experience spontaneous, unprovoked panic attacks, the hallmark of panic disorder, remains controversial. Whether panic disorder occurs in pre-adolescents is still an unresolved issue, but if it does, it must be very scarce (Costello, Egger, & Angold, 2004). This scarcity has limited systematic study.

It has been suggested that, in keeping with the cognitive model of anxiety, children lack the cognitive resources for misinterpreting somatic experiences in a catastrophic fashion, and therefore do not have panic attacks. This conjecture seems unlikely, because panic reactions associated with terror occur in children. It is the sudden unprovoked aspect of panic that seems to be missing in childhood, not the catastrophic reaction. At the same time, it is possible that true panic attacks have age-related clinical variants.

Comorbidity of Childhood Anxiety Disorders

Comorbidity is an important clinical feature because it entails greater dysfunction than either condition alone. Two forms of diagnostic overlap are considered: comorbidity among anxiety disorders, and anxiety disorders with other disorders.

Anxiety Comorbidity

Children referred for treatment exhibit especially high comorbidity among anxiety disorders (Costello *et al.*, 2004). Such patterns likely reflect ascertainment biases. In a large treatment study, social anxiety, separation anxiety and generalized anxiety disorders were each diagnosed in about 60% of children (RUPP, 2001). Comorbidity was particularly elevated in children with generalized anxiety disorder who, in 90% of cases, also had another anxiety disorder. Clearly, comorbidity is less marked in community than clinical samples, but strong comorbidity across anxiety disorders, especially for generalized anxiety or overanxious disorder, is also found in population studies (Anderson, Williams, McGee *et al.*, 1987; Angold *et al.*, 1996; Bird, Canino, Rubio-Stipec *et al.*, 1988; Costello, Simonoff, Pickles *et al.*, 1997; Essau, Conradt, & Petermann, 1999; Fergusson, Horwood, & Lynskey, 1993; McGee, Feehan, Williams *et al.*, 1990; Verhulst, van der Ende, Ferdinand *et al.*, 1997). This high comorbidity has raised questions regarding the diagnostic separation of these three disorders.

Non-Anxiety Disorders

There is unanimous agreement that major depression is highly comorbid with anxiety disorders. The strength of this relationship rivals virtually all others in developmental psychopathology (Angold, Costello, & Erkanli, 1999; Costello, 2004; Costello *et al.*, 2002). Because depression is rarer than anxiety disorders, especially in pre-adolescents, it follows that among those with anxiety the overlap with depression is not as striking as when one selects those with depression, and that this comorbidity increases with age. Although some clinical reports indicate comorbidity between anxiety and attention deficit hyperactivity disorder (ADHD), population-based studies find weak relationships (Angold *et al.*, 1999). There is some evidence of comorbidity between anxiety disorders and substance abuse or conduct disorder (Kaplow, Curran, Angold *et al.*, 2001; Rutter, Maughan, & Kim-Cohen, 2006).

Assessment

The assessment of pediatric anxiety has benefitted from a proliferation of instruments. They include paper-and-pencil rating scales for children, parents and teachers, clinician-rated scales, as well as child and parent interviews. Several reviews have appeared of self, parent and teacher rated anxiety scales for children (Brooks & Kutcher, 2003; Seligman, Ollendick, Langley *et al.*, 2004; Silverman & Ollendick, 2005). Therefore, only an overview is provided.

Rating Scales

Rating scales serve diverse purposes. They may screen large groups to identify children most in need of assistance or to implement prevention programs. Scales may be used for economical reasons, as they provide an economical way for assessments in epidemiological or behavioral genetic studies (Topolski, Hewitt, Eaves *et al.*, 1999). In clinical studies, scales may serve as indices of severity (RUPP, 2003).

Rating scales that anteceded DSM-III and ICD-10 were not designed to reflect the current classification. They comprised factors such as worry, physiological anxiety and fear of bodily harm, as in the Revised Children's Manifest Anxiety Scale (RCMA; Reynolds & Richmond, 1985), the State-Trait Anxiety Inventory for Children (STAIC; Speielberger, 1973) and the Revised Fear Survey Schedule for Children (FSSC-R; Ollendick, Yang, King *et al.*, 1996). The widely used Children's Behaviour Checklist (CBCL; Achenbach, 1991) generates a nonspecific factor of emotional disturbance, called "internalizing" factor. In general, these scales assess constructs distinct from those generated by newer scales.

An important clinical challenge is to differentiate between anxiety and depression, a challenge reflected by the fact that a single unitary factor of the CBCL encompasses both dysfunctions. Many other scales that purport to differentiate anxiety from depression fail to do so (Klein, 1994). The meaning of scale ratings of anxiety is further complicated by the poor agreement between parent or child ratings with information obtained from clinical interviews (RUPP, 2003). It is beyond the purview of this chapter to provide comprehensive discussion of psychometric requirements for diagnostic indices.

Growing interest spurred the development of more diagnostically relevant measures of childhood anxiety. Recent efforts reflect shifts in the classification of anxiety disorders; with greater relevance given to diagnostic groupings. Standardized scales include the Multidimensional Anxiety Scale for Children (MASC; March, Parker, Sullivan *et al.*, 1997; March & Sullivan, 1999) and the Self Report for Child Anxiety Related Disorders (SCARED; Birmaher, Khetarpal, Brent *et al.*, 1997). The MASC and SCARED stand out as promising clinically relevant indices. Both measures demonstrate adequate test–

retest reliability, divergent validity from depression measures, reasonable correlations with clinical ratings of anxiety severity, and sensitivity to treatment effects.

Several anxiety scales are designed for clinicians. The Hamilton Anxiety Scale (HAS; Hamilton, 1969) developed for adults has had limited application in younger populations. In a controlled treatment study, it performed less well than another clinician-rated index, the Pediatric Anxiety Rating Scale (PARS), which taps diagnostic criteria and has good psychometric properties (RUPP, 2003).

Diagnostic Interviews

Diagnostic interviews serve different purposes. The highly structured DISC was developed for epidemiological studies, to be administered by individuals without clinical training or by computer (Shaffer, Fisher, Lucas *et al.*, 2000). Support for the clinical utility of the DISC is mixed. Fair agreement between DISC diagnoses and clinical interviews conducted by the same clinicians led to the claim that the DISC had a role in clinical settings (Schwab-Stone, Shaffer, Dulcan *et al.*, 1996). However, other data do not support the claim. For example, diagnostic rates are high in epidemiological studies using the DISC (Table 39.1). Moreover, other findings question the validity of anxiety diagnoses generated by the DISC (March, Swanson, Arnold *et al.*, 2000).

The Child and Adolescent Psychiatric Assessment (CAPA; Angold & Costello, 2000), highly structured and administered by non-clinicians, is also used in epidemiological studies. Relative to the DISC, the CAPA requires more training and more closely resembles the clinical interview. While CAPA appears promising, the unavailability of data concerning treatment sensitivity precludes endorsement of clinical relevance.

The key issue is whether anxiety disorders generated by structured interviews are valid. Some evidence from longitudinal, family-based and imaging studies points towards validity. However, inconsistent findings concerning the predictive significance of childhood anxiety disorders among girls and boys studied epidemiologically (Costello, Angold, & Keeler, 1999; McGee, Feehan, Williams *et al.*, 1992; Pine *et al.*, 1998) raise questions about the validity of anxiety diagnoses in community samples.

The Kiddie-Schedule for Affective Disorder and Schizophrenia (K-SADS) was developed for use by clinicians and allows full latitude of inquiry. Multiple versions exist, including a highly structured version administered by lay interviewers (Kaufman *et al.*, 1997, 2000). The Diagnostic Interview for Children and Adolescents (DICA; Reich, 2000), also highly structured, has been used in semistructured format. The Anxiety Disorders Interview Schedule for Children (ADIS) allows full clinical inquiry (Silverman, Saavedra, & Pina, 2001). As with other clinically based semistructured interviews, the quality of data depends highly on interviewers' training and qualifications.

There is little to guide the selection of one instrument over another, in terms of better reliability or validity. All have demonstrated modest to adequate test–retest reliability, with anxiety disorders faring no better than mood disorders and slightly worse than behavioral disorders. The major factor informing selection concerns the availability of skilled clinicians for implementation. Although conceived for research purposes, diagnostic interviews may be useful to clinicians because they provide comprehensive coverage of symptomatic status (see chapter 19), and represent excellent teaching tools for training in clinical diagnosis.

Epidemiology of Pediatric Anxiety Disorders

Across several continents, well-executed epidemiological studies delineate key features of anxiety disorders, including prevalence, risk factors and longitudinal outcomes. These studies have the great advantage of avoiding clinical biases introduced by clinical samples.

Prevalence of Childhood Anxiety Disorders

Prevalence studies that have relied on interviews with parents and/or children are presented in Table 39.1. Most report prevalence of broadly conceptualized anxiety disorders. Ongoing epidemiological studies are obtaining DSM-IV and ICD-10 diagnoses. However, most anxiety diagnoses have remained virtually unchanged, so that previous studies are relevant to the current nomenclature.

Most epidemiological studies at all ages find anxiety disorders to be the most common mental disorders. The few population-based studies of panic disorder have found very low rates in children and adolescents, below 1% for lifetime and lower frequencies for the past 6 or 12 months (Pine *et al.*, 1998; Reed & Wittchen, 1998; Verhulst *et al.*, 1997; Whitaker, Johnson, Shaffer *et al.*, 1990). In pre-adolescents, separation anxiety disorder is probably the most prevalent diagnosis (Anderson *et al.*, 1987; Costello *et al.*, 1996, 1999; Costello, Egger, & Angold, 2005; Pine, Cohen, Brook *et al.*, 1998), whereas social anxiety disorder, generalized anxiety disorder or what was previously termed overanxious disorder, increase in adolescence (Fergusson *et al.*, 1993; McGee *et al.*, 1990; Pine *et al.*, 1998; Verhulst *et al.*, 1997). All longitudinal epidemiological studies (Anderson *et al.*, 1987; Costello *et al.*, 2003; Kim-Cohen *et al.*, 2003; McGee *et al.*, 1992; Pine *et al.*, 1998) find an increment in social phobia during adolescence, confirming that the disorder often emerges in adolescence.

Rates of any anxiety disorder within the past 6 or 12 months range widely, from 1.8% in New Zealand (Anderson *et al.*, 1987) to 23.5% in Holland (Verhulst *et al.*, 1997). Variation may reflect true differences as a result of cultural influences. However, disparate rates emerge even when site differences seem minimal. For example, two well-executed studies of adolescents, using similar interviews and both conducted in urban sites in Germany, Bremen (Essau *et al.*, 1999) and Munich (Wittchen *et al.*, 1999), report lifetime rates for social phobia of 1.6% and 4%, respectively. As evident in Table 39.1, another case in point are the New Zealand studies from Dunedin (McGee *et al.*, 1990) and Christchurch (Fergusson

Table 39.1 Prevalence (%) of anxiety disorders in children, adolescents, and adults followed prospectively.

Location	Authors	*n*	Age (years)	Interview	Time frame (months)	Rates (%) Any	SiPh	SAD	OAD	SoPh	PD
New Zealand											
Dunedin	Anderson *et al.* (1987)[a]	785	11	DISC-C[b]	12[c]	1.8–7.5	0–2.4	0.06–3.5	0.05–2.9	0–0.9	–
					12[d]	3.6[x]	1.7	1.9	2.5	0.4	
	McGee *et al.* (1990)[a]	943	15	DISC-C	12[e]	10.7[x]	3.6	2.0	5.9	1.1	–
	Kim-Cohen *et al.* (2003)[a]	976	26	DIS	12[e]	26.1[x]	7.1	–	5.5 (GAD)	10.7	3.9
Christchurch	Fergusson *et al.* (1993)	986	15	DISC-P	12[e]	3.9	1.3	0.1	0.6	0.7	
		965		DISC-C	12[e]	10.8	5.1	0.5	2.1	1.7	
	Goodwin *et al.* (2004)	969	16–18	M-CIDI[i,o]	12[e]	18.4	9.6	–	2.7 (GAD)	7.5	–
		957	18–21	M-CIDI[i,o]	12[e]	14.6	6.5	–	1.8 (GAD)	6.7	–
Germany											
Manheim	Esser *et al.* (1990)	191	13	Graham/Rutter P/C[f,g,m]	6	5.8	–	–	–	–	–
Munich	Reed & Wittchen (1998)[a]	3021	14–24	M-CIDI[h,j]	12	–	–	–	–	–	0.6
					Lifetime	–	–	–	–	–	0.8
	Wittchen *et al.* (1999)[a]	925	14–17	M-CIDI[h,i]	12	–	–	–	–	3.0	–
					Lifetime	–	–	–	–	4.0	–
Bremen	Essau *et al.* (1999)	1035	12–17	M-CIDI[h,i]	Lifetime	–	–	–	–	1.6	–
UK											
London‡	Kramer *et al.* (1998)	131	13–17	K-SADS[i,j]	12	5.3	–	–	3.1	1.5	0.8
Holland	Verhulst *et al.* (1997)	312/780[k]	13–18	DISC-C	6	10.5	4.5	1.4	1.8	3.7	0.2
				DISC-P		16.5	9.2	0.6	1.5	6.3	0.3
				DISC[l]		23.5	12.7	1.8	3.1	9.2	0.4
				DISC[m]		5.3	–	–	–	–	–
						4.4					
Puerto Rico	Bird *et al.* (1988)	386/777[h]	4–16	DISC[m]	6	7.0	2.6	4.7	–	–	–
							1.3	2.1	–	–	–
USA											
Missouri	Kashani *et al.* (1987)	150	14–16	DICA[i,n]	12	8.7	–	–	–	–	–
Pennsylvania	Costello *et al.* (1988)[a]	300/789[k]	7–11	DISC-C	12	10.5	6.7	4.1	2.0	1.0	–
				DISC-P	12	6.5	3.0	0.4	2.8	0	–
	Benjamin *et al.* (1990)[a]	300/789[k]	7–11	DISC[e]	12	15.4	9.1	4.1	4.6	1.0	–
New York State	Pine *et al.* (1998)	776	9–18	DISC[e]	12	–	11.6	8.6	14.3	8.4	0.0
		760	11–20	DISC[e]	12	–	5.9	3.7	8.0	9.9	0.0
		716	17–26	DISC[e]	12	–	22.1	–	5.0 (GAD)	5.6	0.1

New Jersey	Whittaker *et al.* (1990)	356/5596[k]	13–18	Study interview[i]	Lifetime	–	–	–	3.7	–	0.6
Nationwide	Magee *et al.* (1996)	1765	15–24	CIDI[i,o]	Lifetime	–	10.8	–	–	14.9	–
North Carolina	Costello *et al.* (1996)	1015	9, 11, 13	CAPA[i,p]	3	5.7	0.3	3.5	1.4	0.6	0.03
	Costello *et al.* (2003)	1420	9–16	CAPA[i,p]	3	2.4	–	–	–	–	–
Georgia, New Haven New York Puerto Rico	Shaffer *et al.* (1996)	1285	9–17	DISC-P[q,r]	6	21.0	11.7	2.5	4.3	7.9	–
				DISC-C[r]		23.7	11.2	3.1	5.4	8.5	
				DISC[m]		18.5	9.5	4.1	8.0	8.2	–
						13.9	6.8	3.5	6.5	6.6	
				DISCS		20.5	3.3	5.8	7.7	7.6	–
Oregon	Lewinsohn *et al.* (1998)	1709	15.5	KSADS	12	2.8	1.3	0.2	0.5	0.9	0.3
Virginia	Simonoff *et al.* (1997)	2762 (twins)	8–16	CAPA[p,t]	3	–	21.2 4.4	7.2 1.5	10.8 4.4	8.4 2.5	–

OAD, overanxious disorder; PD, panic disorder; SAD, separation anxiety disorder; SiPh, simple phobia; SoPh, social phobia.
* Rates calculated from papers.
‡ Adolescents in primary care clinics.
[a] Same cohort within site.
[b] DISC-C and DISC-P, Diagnostic Interview Schedule for Children, Child and Parent Version (Costello *et al.*, 1984).
[c] Rates vary depending on diagnostic criteria based on DISC-C, and parent and teacher ratings, e.g., diagnostic criteria met: (1) by two of three sources or by one source and symptoms confirmed by at least one other source; (2) by one source but no other source confirms symptoms; (3) by combining symptoms from all three sources.
[d] Percentage meeting diagnostic criteria applying same standards as at age 15 in McGee *et al.* (1992).
[e] Percent meeting criteria based on DISC-C plus parent ratings.
[f] Interview by Graham & Rutter (1968).
[g] Includes anxiety and mood disorders.
[h] M-CIDI, Munich modification of CIDI (Wittchen *et al.*, 1999).
[i] Diagnosis based on interview with adolescent.
[j] K-SADS, Kiddie Schedule for Affective Disorders and Schizophrenia (Ambrosini *et al.*, 1989).
[k] Two stage study: N in stage 2/N in Stage 1.
[l] Percent meeting diagnostic criteria based on interview with parent *or* child.
[m] *Top line:* percentage meeting diagnostic criteria on parent *or* child interview *and* had a C-GAS <61 (Shaffer *et al.*, 1983).
Bottom line: percentage meeting diagnostic criteria on parent *or* child interview *and* had a C-GAS of 61–70.
[n] DICA, Diagnostic Interview for Children and Adolescents (Herjanic & Reich, 1982).
[o] CIDI, Composite International Diagnostic Interview (WHO, 1990).
[p] CAPA, Child and Adolescent Psychiatric Assessment (Angold & Costello, 1995).
[q] DISC Version 2.3 (Shaffer *et al.*, 1996).
[r] Percentage meeting diagnostic criteria only for symptom number, age of onset and duration.
[s] Percentage meeting diagnostic criteria and impairment linked to the specific disorder.
[t] *Top line:* percentage meeting diagnostic criteria.
Bottom line: percentage meeting diagnostic criteria *and* impairment criteria.

et al., 1993). No anxiety disorder is spared discrepancies in prevalence, even when diagnostic definitions are identical and sites appear indistinguishable.

Table 39.1 illustrates clearly that diagnostic rates are reduced sharply if diagnoses are made irrespective of the "extreme distress" criterion, when only impairment is present. Not surprisingly, the one study that compared prevalence as a function of impairment (Shaffer *et al.*, 1996) found that applying an impairment criterion led to a dramatic lowering of prevalence estimates.

Could secular changes affect rates of anxiety disorders? This possibility cannot be ruled out, but does not seem to account for discrepancies across studies, because results do not suggest time-dependent rates of anxiety disorders (Table 39.1). Similarly, could methods for combining informant information contribute to cross-study differences? The low rate of informant agreement in most studies makes this a reasonable possibility. Depending on their age, children contribute varyingly valuable levels of information, and prevalence of anxiety disorders varies as a function of the reporting source (Table 39.1).

It is generally agreed that the answer regarding optimal approach to diagnosis will come from studies that examine the relative accuracy of diagnostic conventions in predicting course, as well as other features such as genetics and biological markers. One study reported that childhood anxiety disorders without impairment are not predictive of difficulties in adolescence, whereas the same is not true for disorders with impairment (Costello *et al.*, 1999). However, these findings were not supported by another study (Pine *et al.*, 2001). Further complicating diagnosis, impairment may occur in subthreshold syndromes (Reed & Wittchen, 1998).

In conclusion, a fair estimate of current prevalence for any pediatric anxiety disorder accompanied by impairment appears to be 5–10%. Additionally, epidemiological studies have been important in confirming that child and adolescent anxiety disorders are associated with significant impairment in multiple functional domains.

Risk Factors

As a result of the impact of referral biases in clinical samples, epidemiological studies provide more precise identification of risk factors. The current section reviews a range of potential risk factors, including demographic factors, various forms of environmental insult or stress, pre-diagnostic manifestations and medical conditions. Because of inconsistent findings and very small numbers of anxiety disorder cases in epidemiological samples, we also review data from clinically based studies.

Gender emerges as the most consistent risk factor for anxiety. Higher rates of most anxiety disorders have been found in females relative to males as early as age 6 (Lewinsohn, Gotlib, Lewisohn *et al.*, 1998). Anxiety in girls may also have greater predictive impact than in boys for later anxiety (Costello *et al.*, 1999; McGee *et al.*, 1992), but findings are not unanimous (Pine *et al.*, 1998).

Little consensus exists regarding socioenvironmental risk factors. Anxiety has been linked to various features, including economic disadvantage, school failure, stressful life events, family dysfunction, single home households, parental emotional problems and low parental education, but no consistent pattern has emerged. Using a quasi-experimental design, Costello, Compton, Keeler *et al.* (2003) did not find that changes in social welfare were associated with changes in rates of anxiety. Negative findings may reflect limitations of epidemiological studies. Although they have the advantage of minimizing referral biases, they typically study relatively small numbers of affected children, often with relatively mild disorders. For example, among 1035 adolescents studied by in one study (Essau *et al.*, 1999), only 17 had social phobia.

Inconsistent associations for socioenvironmental risk factors also emerge in clinical or family-based studies. For example, a recent meta-analysis identified an association between pediatric anxiety and parenting behaviors (Wood, McLeod, Sigman *et al.*, 2003). However, these are non-specific correlates of psychopathology that occur in multiple childhood disorders. Interest in the relationship between pediatric anxiety disorders and adverse social experiences emerges from at least two sets of findings. First, as reviewed below, rodents and non-human primates display developmental plasticity in behavioral and neural responses to threats (Gross & Hen, 2004), as shown by findings that alterations in social experiences produce long-term alterations in stress responses. These data generate questions concerning the degree to which adverse social experiences might shape humans' responses to threats during childhood. Second, children who experienced trauma exhibited marked increases in various anxiety disorders, not exclusively PTSD (Pine & Cohen, 2002; Steinberg & Avenevoli, 2000).

Associations between adverse life events and pediatric anxiety have not been found consistently (Eley & Stevenson 2000; Hankin & Abramson, 2001; Williamson, Birmaher, Dahl *et al.*, 2005). Because most studies are cross-sectional, it remains unclear whether life events represent correlates, as opposed to causes, of anxiety. However, in a longitudinal study, adverse life events in adolescence predicted incidence of future anxiety, with a particularly strong risk in females for generalized anxiety disorder (Pine, Cohen, Johnson *et al.*, 2002). Similar associations have been found among adults, in that the same varieties of psychosocial risk exhibit associations with pediatric and adult anxiety disorders.

Subclinical elevations on anxiety rating scales and personality style questionnaires, such as the Children's Anxiety Sensitivity Index (CASI), have been considered risk factors for anxiety disorders (Pine *et al.*, 2001). Whether such measures reflect current anxiety, as opposed to risk factors, remains controversial (Mannuzza *et al.*, 2002). So far, no data document an association between such scale ratings and future anxiety.

Finally, risks associated with medical conditions have been reported. In the perinatal period, various adversities have been linked to risk for anxiety. These include neurological injury, febrile seizures, low birth-weight, exposure to toxins and minor neurological findings (Breslau, 1995; Breslau & Chilcoat, 2000; Breslau, Chilcoat, Johnson *et al.*, 2000; Shaffer *et al.*, 1985; Vasa *et al.*, 2002; Whitaker *et al.*, 1997). However, as with other risk factors, no consistent findings emerge.

The strongest medical risk factor appears to be respiratory dysregulation. Circumstances that produce recurrent dyspnea predict risk for pediatric anxiety disorders (Goodwin, Pine, & Hoven, 2003; Slattery *et al.*, 2002); associations are particularly strong with asthma, which confers risk for separation anxiety disorder and panic attacks. Cigarette smoking during adolescence also incurs risk for future panic attacks, but not for social anxiety disorder (Johnson *et al.*, 2000). Similar associations have not been found for illicit substances (Rutter *et al.*, 2006). Findings are consistent with other work implicating respiratory dysfunction in separation anxiety disorder and panic disorder.

Kagan, Snidman, McManis *et al.* (2001) noted a relationship between what has been designated as inhibited childhood temperament and later anxiety disorders. Children with inhibited temperament are defined as high reactive during

infancy, behaviorally inhibited and reacting with apprehension to novelty during toddlerhood. They are defined as in the top 15% in delay to speak and smile in novel settings.

Altogether, associations between inhibition and psychopathology have been examined in thousands of children. Findings by Kagan *et al.* suggest an association between behavioral inhibition and later anxiety, with distinct associations at different developmental periods. During school-age years, increased risk occurs for various anxiety disorders, including separation anxiety disorder and phobias. Others find that inhibition at age 3 predicts risk for depression but not anxiety at age 21 (Caspi, Moffitt, Newman *et al.*, 1996).

Associations with anxiety vary in strength and correlations between inhibition and anxiety ratings cross-sectionally, let alone over time, are rarely greater than 0.20–0.40. Hence, the magnitude of associations is at best moderate. However, some evidence suggests particularly strong associations for measures of social anxiety in adolescence (Hayward, Killen, Kraemer *et al.*, 1998; Schwartz, Snidman, & Kagan, 1999). Comparable associations also emerge with shyness in early childhood, and with anxiety in early adolescence, with odds ratios in the moderate range (Prior, Smart, Sanson *et al.*, 2000), as well as for teacher or parent measures of anxious/withdrawn behavior in childhood and anxiety disorders in adulthood (Goodwin, Fergusson, & Horwood, 2004).

Longitudinal Outcome

The long-term consequences of childhood anxiety disorders take on special importance given the high proportion of affected children. The study of diagnostic stability has used community cases, high-risk children and clinic patients, using retrospective and prospective designs.

Seven community-based studies have examined the course of specific anxiety disorders. The first, from Dunedin (Anderson *et al.*, 1987), provides indirect evidence on outcome for individual anxiety disorders (Feehan, McGee, & Williams, 1993; Kim-Cohen *et al.*, 2003; McGee *et al.*, 1992; Poulton, Pine, & Harrington, 2006). In the initial follow-up, from age 11 to 15, a composite index of any mood or anxiety disorder predicted later anxiety for girls, but not boys (McGee *et al.*, 1992). This sex difference was obtained in two other prospective studies (Costello *et al.*, 1999; Rueter, Scaramella, Wallace *et al.*, 1999). The latter also found that emotional symptoms predicted major depression. Further follow-up documents longitudinal associations in anxiety disorders, with little relationship between specific child and adult anxiety disorders. The results from two other community-based studies provide similar evidence of non-specific risk for adult anxiety disorders among adolescents with a range of anxiety disorders (Bittner *et al.*, 2004; Lewinsohn, Zinbarg, Seeley *et al.*, 1997).

Thus, five studies found that anxiety disorders during childhood or adolescence predicted risk for an array of mood or anxiety disorders during adulthood. None documented diagnostic specificity in outcome. Two other studies found evidence of specificity. A school-based study found specificity in the course of social phobia but not separation anxiety disorder across adolescence (Hayward *et al*, 1998). Perhaps the strongest evidence of longitudinal specificity derives from the New York longitudinal study (Pine *et al.*, 1998). From childhood or adolescence to adulthood, specific phobias predicted specific phobia exclusively. Similarly, social phobia was predictive of social phobia exclusively. Separation anxiety disorder predicted no specific disorder, but tended to predict panic attacks, and overanxious disorder was associated with an array of adult disorders including anxiety disorders, but not overanxious disorder, and major depression.

Beyond these community-based studies, evidence of specificity in course also emerged from a prospective high-risk study that followed children of parents with either major depression or panic disorder. Phobias and overanxious disorder, but not separation anxiety disorder, carried a two- to fourfold increase of major depression at follow-up (Weissman, Warner, Wickramaratne *et al.*, 1997). The course of childhood anxiety disorders has also been reported for clinic samples. Two studies ascertained children with school refusal and prominent anxiety symptoms prior to the nosological system introduced in the early 1980s (Berg & Jackson, 1985; Flakerska-Praquin, Lindstoem, & Gillberg, 1997). The majority of children experienced relatively benign clinical courses into adulthood. Three other clinical studies (Aschenbrand, Kendall, Webb *et al.*, 2003; Klein, 1995; Last, Hansen, & Franco, 1997) confirm a relatively low rate of later anxiety disorders in children with anxiety disorders. In the study by Klein (1995), separation anxiety disorder coupled with school phobia predicted panic disorder, as well as major depression, although panic disorder was not a frequent outcome (7% versus 0% in non-anxious comparisons). Another short-term follow-up found an elevated rate of panic disorder only among clinic children with "primary" separation anxiety disorder (Aschenbrand *et al.*, 2003).

In conclusion, data from outcome studies support several observations. Although childhood anxiety disorders show considerable stability, most children with anxiety disorders do not have anxiety disorders or depression in adulthood. However, most adults with anxiety or mood disorders are likely to have a childhood history of anxiety. Evidence of specific risk for adult mood and anxiety disorders is not strong.

Pathophysiology

Family Genetics

Familial aggregation studies have relied on multiple designs, summarized below.

Family Studies

During the past 25 years, more than 20 studies have reported an association between various forms of parental psychopathology and childhood anxiety (Beidel & Turner, 1997; McClure, Brennan, Hammen *et al.*, 2001; Merikangas, Avenevoli, Dierker *et al.*, 1999; Middeldorp, Cath, Van Dyke

et al., 2005; Rende, Wickramaratne, Warner *et al.*, 1995; Turner, Beidel, & Costello, 1987; Warner, Mufson, & Weissman, 1995; Weissman, Leckman, Merikangas *et al.*, 1984). These studies include so-called "top-down" studies, which evaluate children of parents with anxiety or depressive disorders, as well as a handful of so-called "bottom-up" studies, which ascertain parents of children with anxiety disorders. Multiple studies reported higher rates of anxiety disorders in children of parents with anxiety disorders, relative to children of non-ill parents, as shown in Table 39.2. Questions arising from these studies concern the specificity of parent–child concordance for anxiety disorders versus depression, and specificity of aggregation for distinct anxiety disorders (Middeldorp *et al.*, 2005). The weight of the evidence from studies in Table 39.2 suggests non-specificity in the associations, between parental anxiety and depression predisposing and offspring anxiety disorders. Some work provides evidence of specificity for parent–child anxiety disorders aggregation. An association between panic disorder in parents and separation anxiety disorder in offspring is the most consistent finding (Biederman *et al.*, 2001, 2004; Capps, Sigman, Sena *et al.*, 1996). Coupled with data implicating respiratory dysfunction in the two conditions, these data suggest that panic disorder and separation anxiety disorder share an underlying diathesis (Klein, 1993). An association between parental depression and separation anxiety disorder in offspring has also been noted (Biederman *et al.*, 2004). Other data suggest that parental depression is associated with offspring social anxiety disorder, phobias and generalized anxiety disorder, but not separation anxiety disorder (Lieb, Isensee, Höfler *et al.* 2002; Merikangas *et al.*, 1999). Finally, late adolescent rather than adult onset panic disorder may be particularly heritable (Goldstein, Wickramaratne, Howath *et al.*, 1997).

Genetic Studies

In light of consistent cross-generational transmission, attempts have been made to decompose familial transmission into environmental and genetic components. Few studies have been conducted in pediatric anxiety, none using an adoption design and most relying on symptom scales.

Among adults, a growing literature suggests that genetic factors account for approximately 40% of the variability in risk for anxiety, with most of the remaining variance attributed to non-shared environmental factors (Hettema, Neale, & Kendler, 2001; Hettema, Prescott, Myers *et al.*, 2005). These studies provide evidence of both unique and shared liabilities across distinct adult disorders. Generalized anxiety disorder and major depressive disorder appear to share a genetic substrate, and differ largely in contributions from non-shared environmental factors (Hettema *et al.*, 2001). Studies in adolescents suggest similar genetic patterns, with common genes predisposing towards anxiety before puberty and depression after puberty (Silberg *et al.*, 1999; Silberg, Rutter, & Eaves, 2001). Other anxiety disorders appear to have more disorder-specific genetic risk. For example, genetic risk for panic disorder appears distinct from the risk for phobias, generalized anxiety disorder and major depression (Hettema *et al.*, 2005). While not all twin data support specificity, the weight of evidence indicates that adult anxiety disorders are influenced by both disorder-specific and disorder-unique liability factors (Middeldorp *et al.*, 2005).

Genetic influences on anxiety comorbidity has been examined in a large twin study (Hettema *et al.*, 2005). The study found genetic influences to separate two groups of anxiety disorders. One consisted of panic disorder and generalized anxiety disorder, the other of specific phobias. Based on these genetic findings, comorbidity between panic disorder and generalized anxiety disorder is to be expected. Other work in this sample suggests that shared liability to a range of anxiety states may be expressed through underlying personality factors, such as neuroticism (Hettema, Neale, Myers *et al.*, 2006). Extending the search for possible explanations of comorbidity across anxiety disorders, the twin sample was used to test the contribution of neuroticism to the genetic variance in anxiety disorders (Hettema *et al.*, 2006).

In children, divergent estimates of heritability emerge from studies using scale scores (Bolton *et al.*, 2006; Eley *et al.*, 2003; Eley & Stevenson 1999; Eley, Stirling, Ehlers *et al.*, 2004; Topolski *et al.*, 1999). Similar assessment methods have yielded divergent estimates for parent and child rated anxiety scales. Twin data in children are consistent in suggesting a modest genetic component to most forms of childhood anxiety, with heritabilities generally accounting for less than 40% of the variance. These relatively low heritabilities across the age range have led to the suggestion that genes confer a broad diathesis towards anxiety as opposed to a predilection for one or another specific disorder. Consistent with this possibility, heritabilities for temperamental factors, such as behavioral inhibition, have been somewhat higher than those for specific anxiety symptoms or disorders (Goldsmith & Lemery, 2000). Non-shared environmental factors account for much of the remaining variance in child-based twin studies of anxiety symptoms, much as they do in adults. Results in children show variability in genetic and environmental contributions to anxiety. This variability, which may reflect distinct genetic and environmental effects across age, sex and specific forms of anxiety, complicates clear interpretation of the nature of transmission.

As noted in chapter 23, the identification of genes will contribute greatly to our understanding of causal factors. No genomic studies have been conducted in childhood anxiety disorder. In adults, panic disorder, which has been shown to be familial, has been examined for influential genes. Replications have failed. Some suggest that it is futile to expect nosological clarity in psychiatry from genetic findings (Kendler & Greenspan, 2006). It is unlikely that the search for genes in childhood anxiety disorders will fare better than it has for adult anxiety disorders. This failure will limit definitive statements regarding the exact nature of genetic influences, but it will not alter the need to rely on other informative clinical and biological strategies to determine the nosological validity of childhood anxiety disorders.

Table 39.2 Anxiety in children as a function of parental psychopathology.

Author Top down studies	Parental diagnosis (No of offspring)	Odds ratio between parental psychopathology and anxiety disorders in offspring vs. normal controls
Weissman *et al.* (1984)	MDD and PD (19)	10.4*
	(mothers)	2.3
	MDD (23) (mothers)	
Turner *et al.* (1987)	OCD or AGO (16)	7.2*
	Dysthymia (14)	5.5*
Rende *et al.* (1995)	MDD (164)	2.2 T1*; 2.9 T2*
	No MDD (68)	.92 T1; .92 T2
Warner *et al.* (1995)	MDD (32)	2.5*
	MDD and PD (60)	1.1
	PD (17)	2.3*
Capps *et al.* (1996)	AGO (16)	3.9*
Beidel & Turner (1997)	AD (28)	5.4*
	MDD (24)	5.7*
	AD and MDD (29)	5.4*
Merikangas *et al.* (1999)	AD, AGO and OAD (36)	2.5
Biederman *et al.* (2001)		(≤2 anxiety disorders)
	PD and MDD (141)	8.2*
	MDD (46)	4.3
	PD (26)	8.8*
	No PD or MDD (99)	–
McClure *et al.* (2001)	Anxiety, no MDD (40 in mother)	3.1* (anxiety in child)
		1.6 (anxiety in child)
	MDD, no Anxiety (248 in mother)	3.6* (anxiety in child)
	Anxiety and MDD (110 in mother)	
Biederman *et al.* (2004)		(≤2 anxiety disorders)
	PD and MDD (56)	2.3* (anxiety in child, PD in parent)
	MDD (132)	1.3 (anxiety in child, MDD in parent)
	PD (55)	
	No PD or MDD (491)	
Pine *et al.* (2005)	PD and MDD (41)	4.9* (anxiety in child, PD in parent)
	MDD (53)	4.8* (anxiety child, MDD in parent)
	PD (24)	
	No PD or MDD (26)	

Author Bottom up studies	Children's diagnoses (No of mothers)	Odds ratio between parental psychopathology and anxiety disorders in offspring vs. normal controls
Last *et al.* (1991)	SAD (19)	With PD in 1.4 (SAD in child)
	OAD (22)	Parents 4.2* (OAD in child)
	OAD and SAD (17)	10.7* (OAD & SAD in child)
Leib *et al.* (2000)	SoPh ($n = 58$)	With SoPh 4.7* (parent SoPh) in child 3.5* (parent other anxiety) 3.6* (parent depression)

Parental diagnoses: AGO, agoraphobia; MDD, major depression; OCD, obsessive compulsive disorder; PD, panic disorder.
Offspring diagnoses: AD, anxiety disorder including PD, OCD or social phobia; GAD, generalized anxiety; OAD, overanxious disorder; SAD, separation anxiety.
T1, time one; T2, 2-year follow-up.
* 95% Confidence interval of odds ratio excludes 1.0 (i.e., statistically significant at $P \leq 0.05$).

Endophenotypes

Research has begun to move beyond examination of familial aggregation in anxiety symptoms to the study of underlying mechanisms. Anxiety is viewed as a downstream manifestation of genetically based perturbations in neural function that do not directly map on to diagnostic categories. Rather, they cause abnormalities in information processing that lead to psychopathology.

The term "endophenotype" has been used to describe heritable abnormalities in neural function and associated information-processing capacities (Gottesman & Gould, 2003). Endophenotypes show independent associations with psychiatric disorders and with their risk factors. Strong evidence for potential endophenotypes is scarce; working memory abnormalities in schizophrenia probably represent the most compelling example in psychiatry.

Three lines of work provide preliminary data on potential endophenotypes in pediatric anxiety disorders. First, behavioral inhibition has been conceptualized as an endophenotype. Longitudinal studies note associations with anxiety disorders, and family studies with parental panic disorder (Kagan *et al.*, 2001). This work views temperament and anxiety as alternative manifestations of perturbations in the brain's fear circuit. However, because behavioral inhibition may also be associated with parental depression, there may not be diagnostic specificity in this relationship (Caspi *et al.*, 1996; Rosenbaum *et al.*, 2000). In addition, some suggest that behavioral inhibition represents manifest psychopathology, as opposed to a risk factor or endophenotype. An intervention study found stronger treatment effects on anxiety symptoms than on behavioral inhibition (Rapee, Kennedy, Ingram *et al.*, 2005), supporting the endophenotype perspective for behavioral inhibition.

Second, some work implicates enhanced autonomic reactivity in risk for anxiety (Grillon, Dierker, & Merikangas, 1997; Merikangas *et al.*, 1999). As with behavioral inhibition, reactivity-based endophenotypes are presumed to result from perturbations in fear-circuit function. Particular interest has focused on measures of hypothalamic–pituitary–adrenal (HPA) axis activity, although such findings in pediatric anxiety disorders are inconsistent (Terleph *et al.*, 2006). Third, information-based approaches suggest that abnormal attention regulation during threat exposure may represent an endophenotype (Pine *et al.*, 2005). Attention-processing abnormality to threat, also presumed to result from fear-circuit dysfunction, has been linked to both pediatric anxiety disorders and parental panic disorder.

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Molecular Genetics

Studies of molecular genetic correlates have extended the modern view of psychopathology as the result of circuitry-based perturbations in information processing. Perspectives on psychiatric genetics have advanced considerably in the past 10 years, to the point where most common forms of psychopathology, including pediatric anxiety disorders, are viewed as so-called "complex disorders." Such conditions are caused by panoplies of genetic and non-genetic factors, each making relatively small contributions to the phenotype.

In anxiety disorders, the most productive research has attempted to link specific genetic polymorphisms to neural and cognitive dysfunction. Virtually all work on anxiety is of adults. Current findings implicate a polymorphism of the serotonin transporter gene in fear circuitry dysfunction (Hariri *et al.*, 2002). Other work, again largely in adults, suggests that such genetically based perturbations predispose to psychopathology through interactions with environmental risk (Caspi *et al.*, 2003). Although much of this work examines associations with adult depression, it is relevant to pediatric anxiety disorders, given their associations with adult depression. Two studies have reported a gene–environment interaction with the serotonin transporter in pediatric depression (Eley *et al.*, 2004; Kaufman, Douglas-Palumberi, Houshyar *et al.*, 2004), and another found such an interaction for behavioral inhibition (Fox *et al.*, 2005). Behavioral inhibition also has been linked to a polymorphism in the gene for corticotropin-releasing factor (CRF), a key regulator of HPA function (Smoller *et al.*, 2005). Such an association is consistent with data implicating HPA axis function in fear-circuit activity (see p. 000).

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Psychobiology

Neural Circuitry in Animals

Advances in basic science have altered theories of anxiety disorders. They are viewed as reflecting individual differences in neural function: pediatric anxiety disorders are hypothesized, by some, to result from abnormalities in physiological systems implicated in animal models of anxiety (Gross & Hen, 2004). This view has led investigators to target various physiological systems in an effort to document psychobiological substrates of anxiety.

Animal models of anxiety benefit from strong cross-species conservation in brain circuitry and pharmacology. Distinct forms of fear are regulated by inter-related brain systems involving the prefrontal and medial temporal lobes. Perhaps the best understood phenomena are learned fears, which can be modeled by "fear conditioning" experiments, where an aversive stimulus, such as a shock, is paired with a neutral stimulus, such as a light. Following such pairings, an organism exhibits fear of the formerly neutral stimulus. Learned fear depends upon a neural circuit involving the amygdala, a bilateral collection of individual nuclei located within the brain's medial temporal lobes (LeDoux, 2000). Learning to fear a previously harmless stimulus involves changes in neural function within the basolateral nucleus of the amygdala, and expression of this learning involves output through the central nucleus. Similarly, the process of extinction, whereby a feared stimulus no longer elicits a fear response, requires communication between the amygdala and frontal cortex, and perturbations in extinction reflect aberrant communication between these regions (Quirk & Gehlert, 2003).

Other forms of fear develop without prior learning and are regulated by distinct but related neural circuits. For example, nocturnal organisms such as rodents fear well-lit environments

(Davis, 1998). Unlike learned fears, this fear does not extinguish and may actually increase with repeated exposure. Unlearned fear involves the basolateral but not the central nucleus of the amygdala; the two circuits are regulated by distinct neurochemical systems. For example, infusions with CRF may potentiate unlearned fear, but not conditioned fear.

Neural Development and Fear

The mature fear circuit reflects long-term influences of early-life rearing environment. A wealth of investigations with rodents shows that alterations in maternal care produce long-term changes in the threshold for engaging the medial temporal lobe and prefrontal components of the fear circuit (Meaney, 2001). These effects arise through non-genomic influences, involving DNA methylation. Specifically, functional aspects are altered for genes involved in regulation of the medial temporal lobe and frontal cortex. Work in non-human primates demonstrates comparable associations between rearing and threat responses (Suomi, 2003). These influences appear also for indices of HPA axis function, generating interest in the relationship between HPA axis function and pediatric anxiety disorders. Much of the scientific interest in rearing effects was based on the implicit assumption of permanent scarring. However, the influence of early life experiences is complicated. For example, over 900 genes are regulated by maternal care (Weaver, Meaney, & Szyf, 2006). Moreover, some effects of rearing on genes are reversible. Further complicating an understanding of effects of early rearing, Mathew *et al.* (2002) not only failed to replicate increased cerebrospinal fluid (CSF) CRF in primates raised under stress, but obtained diametrically opposite results (Mathew *et al.*, 2002). In sum, the effects of early maternal behavior and stress on later functions are highly complex, indirect and not regularly irreversible.

Another approach uses anatomic, neurochemical and genetic manipulation to demonstrate developmental plasticity in the fear circuit. Lesion studies in non-human primates find distinct effects of amygdala lesions on fear-related behaviors in mature relative to immature primates (Amaral, 2002). Genetic and chemical manipulations in rodents produce long-term alterations in fear-related behaviors and associated neural circuitry among immature mice, but not in mature mice exposed to the same manipulations (Gross & Hen, 2004). Altogether, animal data suggest that function of the mature fear circuit reflects influences during childhood on fear-circuit development, but the nature of these influences is likely to be highly complex.

Human Physiology and Neural Circuitry

Functional aspects of brain circuits that regulate learned and innate fears can be elicited reliably in lower mammals as well as humans, through changes in physiological indices; of these, the startle reflex has the best understood neuroanatomic circuit. The reflex is augmented by presentations of mildly stressful stimuli. The neural circuit involved in fear conditioning in rodents is thought to mediate augmentation of this reflex in humans.

Adults with various forms of anxiety exhibit startle abnormalities (Grillon, 2002; Grillon & Baas, 2003). Asymptomatic children of parents with anxiety disorders also have been found to have abnormalities in startle regulation (Grillon *et al.*, 1997, 1998). Problematically, startle abnormalities reported in at-risk offspring have not been found in youth with anxiety disorders. In addition, startle abnormalities occur in offspring at risk for anxiety and for depression as well, raising questions about the specificity of associations between abnormal startle and anxiety (Grillon *et al.*, 2005).

Kagan *et al.* (2001) suggests that behavioral inhibition, a marker of risk, results from abnormalities in the same brain circuits implicated in startle potentiation, based on peripheral physiological profiles, using indices influenced by circuits that regulate fear in mammals. In spite of parallels in neural circuits of fear regulation in humans and animals, there are crucial pharmacological inconsistencies. For example, medications effective in panic disorder do not affect fear conditioning, although they appear to affect certain forms of unlearned fear (Blanchard, Griebel, Henrie *et al.*, 1997; Cassella & Davis, 1985). Moreover, associations between fear conditioning and clinical anxiety disorders are marginal at best (Lissek *et al.*, 2005). Accordingly, risk for anxiety disorders has been hypothesized to relate to failures in extinction, or to inherited tendencies to respond to innate unlearned fearful stimuli, rather than to abnormalities in fear-learning per se.

The most developed line of research examines respiratory dysregulation in panic disorder (Klein, 1993, 1996). Much like a well-lit room for a rodent, respiratory stimulants represent unlearned fear-inducing stimuli for air-breathing organisms, including humans. A wealth of evidence suggests that sensitivity to respiratory stimulants identifies individuals with a diathesis for types of anxiety closely related to spontaneous panic attacks. For example, adults with panic disorder have enhanced responses to respiratory stimulants, such as CO_2, sodium lactate, cholecystokinin or doxapram. Sensitivity to CO_2 has also been found in children with anxiety disorders, specifically separation anxiety disorder, but not those with social anxiety disorder (Pine *et al.*, 2005). Syndromes such as subclinical panic disorder that have strong familial associations with panic disorder are also characterized by enhanced responses to respiratory stimulants. Moreover, in adults, signs of respiratory abnormalities, such as enhanced sensitivity to CO_2, occur especially among panic patients with high familial loading (Horwath *et al.*, 1997). In addition, healthy adult first-degree relative of panic patients also exhibit enhanced responses to respiratory stimuli (Coryell, Fyer, Pine *et al.*, 2001); however, CO_2 sensitivity was not found among offspring at risk for panic disorder (Pine *et al.*, 2005).

Cognition and Anxiety

Cognitive processing, specifically memory and attention, is preferentially mobilized by perceived threats, presumably due to the responses' adaptive value. Brain imaging which has been used to delineate fear-circuit dysfunction in anxiety susceptibility has focused on threats' abilities to disrupt strategic

control of attention or attention orienting (Davis & Whalen, 2001). Two procedures have been common to probe threat-related effects on cognitive processes in humans. One relies on the "emotional Stroop test," which taps disruption of strategic attention control. Latencies increase when naming colors of "threat" words as opposed to "neutral" words (Williams, Mathews, & McLeod, 1996). Adults with various anxiety disorders show relatively prolonged latencies to name color of "threat" words, such as "panic," presumably because of enhanced vigilance to them. In the second procedure uses the dot-probe test, which measures attention orienting. Reaction time to a spatial probe is quantified as a function of the proximity of the probe to "threat" words or pictures (Bar-Haim, Lamy, & Pergamin, 2007; Mogg & Bradley 1998). Adults with anxiety show faster reaction times to probes proximal to threatening stimuli, an effect attributed to enhanced vigilance to threats. In both procedures, there are relatively subtle but consistent positive associations between adult anxiety and reaction times to threat presentations. Some evidence suggests similar effects in childhood anxiety disorders (Monk *et al.*, 2006; Pine *et al.*, 2005c).

Beyond these two procedures, other less frequently used indices quantify attentional resources during self-monitoring of attention states. In adolescents an association has been reported between aberrant anxiety-state monitoring with anxiety disorders as well as panic disorder in their parents (Pine *et al.*, 2005). Finally, diagnostic specificity of cognitive biases is in question, because biases have also been found in depression. In addition, cognitive bias for threat does not appear to be a marker of risk because it occurs primarily in symptomatic adults and disappears with treatment (Williams *et al.*, 1996). Nevertheless, manipulating bias experimentally has been shown to alter adults' stress responses (MacLeod, Rutherford, Campbell, *et al.* 2002).

Brain Imaging

Two imaging procedures have been used in pediatric anxiety disorders, neuromorphometry, which examines brain structure, and functional magnetic resonance imaging (fMRI), which reflects blood flow changes during cognitive processes.

Two sets of studies have compared brain structure in pediatric anxiety disorders with healthy comparisons. The first, which examined 10 adolescents with generalized anxiety and healthy comparisons (De Bellis *et al.*, 2000a, 2002), found larger volumes in patients'amygdala and superior temporal gyrus. The second study involved 15 adolescents with mixed anxiety disorders (Millham *et al.*, 2005). Consistent with findings in adults, this study found reduced amygdala volume in pediatric anxiety disorders, particularly in generalized anxiety disorder. The difference disappeared after successful treatment. Three fMRI studies report amygdala activity in pediatric anxiety disorders or related states in response to facial photographs. One study found enhanced amygdala activation during the viewing of evocative face-emotion displays (Thomas *et al.*, 2001). These findings, consistent with those in adults, implicate amygdala hypersensitivity in some forms of anxiety. The second study found no increased amygdala activation in anxious adolescents but observed enhanced activation in the ventral prefrontal cortex, a region implicated in extinction (Monk *et al.*, 2006). Moreover, prefrontal cortex activity correlated negatively with anxiety severity in patients, suggesting that anxiety reflects perturbed functioning in a distributed neural circuit regulated, in part, by the prefrontal cortex. A final study compared amygdala activity in adults classified as inhibited or not inhibited in childhood (Schwartz, Wright, Shin *et al.*, 2003). Enhanced amygdala activity was found in the formerly inhibited individuals, implicating amygdala function in risk for anxiety.

Treatment

Distress and impairment engendered by anxiety disorders and their long-term liability highlight the need for effective treatments. Some interventions, such as cognitive–behavior therapy (CBT), are based on a theoretical model of anxiety; others, such as selective serotonin reuptake inhibitor (SSRI) medications, follow from demonstrated efficacy in adult anxiety disorders. The literature is replete with case studies reporting efficacy for treatments. The review is of systematic controlled trials.

Psychotherapy

CBT is the best-studied intervention. Because CBT is based on the notion that distorted cognitions underlie anxiety symptoms, aspects of many CBT treatments focus on the child's thought processes, aiming to replace negative beliefs with more realistic neutral cognitions. Some CBT treatments recruit the family's active involvement to facilitate exposure. The contribution that parents can make in treatment is likely to vary as a function of the child's disorder and age.

A major positive feature of CBT is the availability of treatment manuals. CBT has been compared with no-treatment waitlist controls (Kendall, 1994; Kendall *et al.*, 1997) or a non-specific control intervention (Beidel, Turner, & Morris, 2000; Last, Hansen, & Franco, 1998; Silverman *et al.*, 1999). While often used in psychotherapy trials, the use of waitlist controls is methodologically problematic when applied to clinic patients. This disposition confirms to patients that they require treatment but it is withheld. Not only might such an intervention fail to help anxiety, it may have a deleterious impact. The most informative studies are those that have relied on a credible comparison treatment. Finally, it is essential that treatment outcome be evaluated by individuals who are not aware of the treatment delivered, rather than by the therapist. In this fashion, one ensures that biases introduced by treatment allegiances do not influence estimates of outcome. These design features are very infrequently met in current studies of psychotherapy in anxiety disorders.

CBT was examined in two systematic studies by Kendall (1994) and Kendall *et al.* (1997). Children received CBT for 16 weeks, or were on a waitlist for 8 weeks before then receiving CBT. In both trials, relative to the waitlist, CBT was

significantly superior. Moreover, sustained reductions in anxiety continued over several years. Waitlist controls have been used in other studies of CBT; only three studies used "attention" controls (Beidel *et al.*, 2000; Last *et al.*, 1998; Silverman *et al.*, 1999), with one finding efficacy for CBT in social phobia (Beidel *et al.*, 2000). Other studies have examined variations in treatment, providing preliminary evidence that either parental involvement (Mendlowitz *et al.*, 1999) or a group-based format (Barrett, Dadds, & Rapee, 1996) may lead to particularly high rates of response. Finally, on the basis of a systematic trial of group CBT, group family CBT and waitlist control, one study concluded that CBT could be implemented effectively in a group format (Barrett, Duffy, Dadds *et al.*, 2001). While results show that CBT produces significant gains in children with anxiety disorders, considerable more work is needed, particularly with credible control conditions.

A recent comparative efficacy study raises major unanticipated questions on the comparative efficacy of CBT, relative to pill-placebo and SSRI medication, in the treatment of adolescent depression (March *et al.*, 2004). These findings emphasize the need for a comparable large-scale CBT/SSRI study in anxiety disorders. Such a study in child anxiety disorders is ongoing and the results should be forthcoming.

The success of CBT in the treatment of impairing anxiety disorders has raised questions on the role of this treatment for prevention. Attempts to use CBT preventatively have typically relied on what is termed "secondary" prevention, whereby children with mild anxiety receive CBT. While results generally suggest that CBT reduces anxiety symptoms in such groups (Rapee *et al.*, 2005), whether results apply to primary prevention is unclear. These interventions have been shown to work in children in the preschool years and onwards. Because children with symptoms are targeted in this work, such interventions might be characterized as therapeutic rather than preventive. Far less work has used alternative approaches, targeting broader portions of the population independent of mild symptoms or other risk factors.

Pharmacotherapy

SSRIs have documented efficacy in virtually all adult anxiety disorders. Four placebo-controlled trials have been published for SSRIs in pediatric anxiety disorders. The first large multisite 8-week study found that fluvoxamine was superior to placebo in children with either social anxiety, separation anxiety or generalized anxiety disorders (RUPP, 2001). Another large study demonstrated comparable benefit for paroxetine over placebo, in children and adolescents with social anxiety disorder (Wagner *et al.*, 2004). Finally, two modest-sized studies demonstrated efficacy for fluoxetine and sertraline, each relative to placebo (Birmaher *et al.*, 2003; Rynn, Siqueland, & Rickels, 2001).

Concern about SSRIs emerged in 2002–2004, following reports that SSRIs were associated with twofold increase in suicidal ideation or behavior, relative to placebo treatment (approximately 4% versus approximately 2%). This observation led to cautionary statements from regulatory officials in Europe and the USA, although debate continues concerning the significance of these data (Vasa, Carlino, & Pine, 2006). Diagnosis did not moderate this association, suggesting that concerns might apply equally to anxiety and mood disorders. A previous literature review (Klein & Pine, 2002) indicated that there was inconsistent support for the efficacy of tricyclic antidepressants in children with separation anxiety. Finally, although there have been some reports on the use of benzodiazepines in anxious children (Klein & Pine, 2002), the efficacy and safety profile of the SSRIs weaken consideration of benzodiazapines.

Conclusions

Multiple findings have documented the importance of childhood anxiety disorders. These include their elevated prevalence, their associated impairment, the fact that they put children at risk for later depression and their moderate but significant continuity with anxiety disorders in adulthood.

Epidemiological studies have generated divergent rates of current anxiety disorders. The evidence suggests 5–10% point prevalence in the general population, with girls over-represented. Some have found greater stability of anxiety in girls than boys. Childhood anxiety disorders predict adult anxiety and depression, but no other psychopathology.

Knowledge of antecedents would enable identification of children at risk and the development of preventive efforts. Few antecedents have been established. Early inhibited temperament is weakly related to later anxiety, especially social phobia. A modest influence for genetic transmission has been found, with non-shared environmental factors having a greater role. The non-genetic factors in childhood anxiety disorders are poorly understood. As a result, they make little contribution to the clinical management of children with anxiety disorders.

Models of brain circuits that regulate fear in animals, also studied in adults, are being applied to children. Early studies suggest that children show abnormalities in underlying fear circuitry, as measured by startle responses to unconditioned fear stimuli, and information processing of fear-related stimuli. However, it is difficult to determine which is cause and which is effect. Neuroimaging studies have focused on the hypothesis of amygdale involvement in anxiety. At this time, the best-documented biological feature of childhood anxiety is respiratory dysregulation, as indexed by hypersensitivity to CO_2 exposure in children with separation anxiety disorder.

Treatment of anxiety disorders encompasses psychotherapeutic and psychopharmacological interventions. Most treatment studies have included a mixture of anxiety disorders. Most behavioral treatment studies have methodological limitations, but there is evidence of short-term and sustained improvement. SSRIs have been shown effective in childhood anxiety disorders. Treatments based on empirical evidence can now be offered to children with anxiety disorders.

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