Anxiety Disorders

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ANXIETY

Anxiety can be defined as the apprehensive anticipation of future danger or misfortune accompanied by a feeling of dysphoria or somatic symptoms of tension. The focus of anticipated danger may be internal or external (DSM-III-R, 1987). It is the uneasiness associated with the anticipation of danger or perceived rejection and loss of love. Anxiety, an emotion, is the subjective sensation that accompanies the body's response to real or perceived threat. All individuals experience some degree of real or perceived threat, and, therefore, we all have had the sensation of anxiety. Fears and anxieties of a mild and transient nature are part of normal development, though this expectation may mask the presence of emerging or existing anxiety disorder (Zahn-Waxler et al., 2000). For some individuals, however, the frequency, duration, intensity, or context of the anxiety is extreme and can interfere with normal development and functioning. These individuals are considered to have anxiety disorders.

Anxiety disorders are the most common psychiatric syndromes in children and adolescents, with estimated point prevalence of 3% to 13% (Kashani and Orvaschel, 1988, 1990). There is a much higher prevalence of anxiety disorders in medical and psychiatric settings. The disability and impairment in health-related quality of life due to anxiety disorders can be severe (Beidel et al., 1991; Francis et al., 1992; Strauss et al., 1988). Feelings of worthlessness, low self-esteem, and difficulties with concentration and motivation are common in anxiety disorders, and these symptoms along with core symptoms of fear and anxiety impair school performance. These symptoms also strain relationships with peers and family members leading to poor social life. In addition, anxiety disorders may interrupt educational attainment and thus affect human capital accumulation and future earnings. Longitudinal data of children with anxiety conditions indicate that anxiety disorders can be chronic and disabling, and they can increase risk of comorbid disorders (Pine et al., 1998). Reports in the adult literature also demonstrate the risk for lifelong impairment, reduced quality of life, and increased rates of suicidality (Katzelnick et al., 2001). Rates of anxiety increase as children move into adolescence, which can adversely affect their development.

Scientific efforts to classify abnormal anxiety symptoms resulted in the clustering of similar clinical presentations of anxiety symptoms into anxiety disorders. The *Diagnostic and Statistical Manual of Mental Disorders,* Third Edition, Revised (DSR-III-R) recognized two child-specific anxiety disorders: separation anxiety of childhood and overanxious disorder of childhood (DSM-III-R, 1987). It also recognized that anxiety disorders occur in both children and adults, such as panic disorder, agoraphobia, specific phobias (e.g., social phobia), posttraumatic stress disorder (PTSD), and obsessive-compulsive disorder (OCD). Although each of these disorders had distinguishing clinical phenomenology, profound anxiety was the core symptom common to all. With DSM-IV (American Psychiatric Association, 1994) and DSM-IV-TR, there has been a refinement of this phenomenology.

PHENOMENOLOGY, CLASSIFICATION, AND DIAGNOSIS

Anxiety is a universal feeling experienced by all. It is thought to be a safety mechanism designed to prepare an individual for flight or fight in reaction to perceived risk or damage. At mild to moderate levels, anxiety may be a useful and adaptive mechanism. At extreme levels, however, it is usually maladaptive and debilitating. One means of judging whether a patient has an anxiety disorder is whether the response of an individual is proportionate to the presenting stressor or anxiety-provoking stimulus.

Numerous physiological changes take place in association with anxiety. These changes may present as many signs and symptoms of anxiety disorders involving many organ systems. A sense of palpitations, tachycardia, increased

blood pressure, and flushing or pallor may be seen. A subjective sense of shortness of breath and an increased respiratory rate can be seen. Blotching of the skin, rashes, changes in skin temperature, and increased perspiration may be noted. Patients may demonstrate tremulousness, muscle tension, and cramping. Patients may have gastrointestinal symptoms such as by diarrhea, nausea, bloating, and abdominal pain. Additional nonspecific physical symptoms such as headache, chest pain, insomnia, dizziness, fainting, and urinary frequency may be observed.

Patients may also present with psychological and cognitive symptoms such as worrying and reports of feeling scared, feeling tense, nervous, or stressed. In states of panic, patients may express a fear of dying, a fear of imminent disaster, or the feeling that one is going crazy. Patients may be easily startled or hyperaroused and may show behavioral symptoms with significant social impact, such as appearing dependent, needy, clingy, shy, withdrawn, and uneasy in social situations. Individuals with anxiety disorders may appear nervous and high strung.

Children and adolescents with anxiety disorders can have a clinical picture that is somewhat different from those seen in adults. For instance, children may not report any worries or anxieties but may have pronounced physical symptoms. Severe tantrums may be their only manifestation of anxiety problems and thus can be confused with mood disorders or oppositional behavior. Anxiety-related tantrums may occur in children who may be generally compliant and cooperative but then unexpectedly have a severe tantrum. These tantrums can be extraordinarily long and involve the child demanding that the guardian help her or her to avoid an anxiety-provoking situation or stimuli. Examples of such tantrums include a child with social phobia (SP) having a temper tantrum to avoid school or children with obsessive-compulsive disorder (OCD) having a tantrum to avoid breaking a ritual or seek parental assistance with cleaning up. Some children present to the pediatrician with physical symptoms such as nausea, stomachache, or headache occurring on Monday morning or Sunday night, which may represent separation anxiety disorder. Children with generalized anxiety disorder (GAD) may feel sick after the news of a thunderstorm or natural disaster.

The diagnosis of normal versus abnormal anxiety largely depends on the degree of distress and its effect on a child's functioning in life. The degree of abnormality must be gauged within the context of the child's age and developmental level (Table 14.1). The following section delineates the diagnostic rubrics utilized to describe anxiety disorders.

TABLE 14.1
NORMAL DEVELOPMENTAL ANXIETY AND ITS COMMON CAUSES

0–6 Months	Loud noises, rapid position changes, rapidly approaching unfamiliar objects
7–12 Months	Strangers, unfamiliar objects, confrontation with unfamiliar people
1–5 Years	Strangers, storms, animals, dark, loud noises, toilet, monsters, ghosts, insects, bodily injury, separation from parents.
6–12 Years	Bodily injury, disease, ghosts, supernatural beings, staying alone, criticism, punishment, failure
12–18 Years	Tests and examinations, school performance, bodily injury, appearance, peer scrutiny and rejection, social embarrassment

SEPARATION ANXIETY DISORDER (SAD)

Separation anxiety is characterized by excessive anxiety or fear concerning separation from home of from those to whom the child is attached. By definition, it begins before age 18 (DSM-IV-TR, 2000). The disorder usually manifests to the clinician with somatic complaints that the child experiences when there is impending separation from home or the parents, such as going to school. The child can have difficulty when left with relatives, day care providers, babysitters, and other caregivers. This disorder also frequently involves refusal to attend sleepovers or outings requiring a separation from parents. Children who have severe symptoms may refuse to sleep in their own rooms or refuse to go to school, leading to significant impairment. Sunday night and Monday morning illnesses are typical in these children, who may feel great on Fridays and weekends. These children have a difficult time going back to school after holiday breaks and especially after summer vacations. Separation anxiety should be distinguished from social phobia, in which the child avoids school because of a fear of being scrutinized by peers. AQ1

Separation anxiety disorder is associated with the development of subsequent depression and panic disorder (McCauley et al., 1993; Mitchell et al., 1988). As it may be an antecedent to subsequent pathology and causes significant distress, appropriate diagnosis and treatment is necessary (Labellarte et al., 1999).

GENERALIZED ANXIETY DISORDER (GAD)

This disorder was referred to as "overanxious disorder of childhood" in previous versions of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM). Generalized anxiety disorder can be defined as excessive worry, apprehension, and anxiety occurring most days for a period of 6 months or more that involves concern over a number of activities or events (DSM-IV-TR, 2000). The focus of the worry and fear is not a specific stimulus as it is in other anxiety disorders such as the extreme anxiety in social situations in social phobia. The person has difficulty controlling the anxiety, which is associated with at least one of the

following: restlessness, feeling "keyed up" or on edge; being easily fatigued; difficulty concentrating or having the mind go blank; irritability; muscle tension; or difficulty falling asleep or staying asleep, or restless sleep. The anxiety causes significant distress and impairs functioning.

PANIC DISORDER

Panic disorder is different from panic attacks; panic attacks are defined as sudden, discrete episodes of intense fear or discomfort accompanied by 4 out of 13 bodily or cognitive symptoms, often manifesting with an intense desire to escape, feeling of doom or dread, and impending danger (DSM-IV-TR, 2000). These symptoms peak within 10 minutes and often subside within 20 to 30 minutes. The 13 symptoms are heart palpitations or fast heart rate; sweating; trembling or shaking; shortness of breath or smothering; choking sensation; chest discomfort or pain; nausea or abdominal distress; feeling dizzy, lightheaded, faint, or unsteady; feelings of unreality or being detached from oneself; fear of losing control or going crazy; fear of dying; numbness or tingling sensations; and chills or hot flashes. Panic disorder consists of recurrent unexpected panic attacks with interepisode worry about having others; the panic attacks lead to marked changes in behavior related to the attacks. Panic attacks are frequently associated with agoraphobia (the fear of the marketplace or public places and avoidance of situations from which escape might be difficult or help might not be available and often experienced as a fear of leaving the home). Although agoraphobia can occur alone, it most often occurs in the presence of panic disorder.

OBSESSIVE-COMPULSIVE DISORDER (OCD)

This disorder is defined by persistent obsessions (intrusive, unwanted thoughts, images, ideas, or urges) or compulsions (intense, uncontrollable repetitive behaviors or mental acts related to the obsessions) that are noted to be unreasonable and excessive (DSM-IV-TR, 2000). These obsessions and compulsions cause notable distress and impairment and are time consuming (more than 1 hour a day). The most common obsessions concern dirt and contamination, repeated doubts, need to have things arranged in a specific way, fearful aggressive or murderous impulses, and disturbing sexual imagery. The most frequent compulsions involve repetitive washing of hands or using handkerchief/tissue to touch things; checking drawers, locks, windows, and doors; counting rituals; repeating actions; and requesting reassurance. Eighty percent of subjects suffering from OCD have both obsessions and compulsions.

Young children with OCD may not recognize their obsessive thoughts or the compulsions and rituals as problematic or unusual. Therefore children between 4 and 10 may frequently have severe tantrums with atypical precipitants as the chief complaint. A child might be usually very compliant, but have a tantrum if asked to speed up his or her cleaning. Young children may also be unable to verbalize their obsessions, but parents can describe avoidance behaviors, compulsions, and rituals.

Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS) are a group of disorders that are believed to be the result of an autoimmune response to group A beta-hemolytic streptococcal infections (Swedo et al., 1998). These disorders can present with tics and obsessions and compulsions. The onset of OCD symptoms is typically more abrupt if associated with PANDAS.

POSTTRAUMATIC STRESS DISORDER (PTSD)

In this disorder, a person experiences, witnesses, or is confronted by a traumatic event or events that involve an actual or perceived threat of death or serious bodily injury, and the person's response involves intense fear, helplessness, or horror. In children, probably the most common traumatic event is abuse. The traumatic event is continually re-experienced in the following ways: recurrent and intrusive distressing remembrances of the event involving images, thoughts, or perceptions; distressing dreams of the event; acting or believing that the traumatic event is recurring; intense anxiety and distress to exposure to situations that resemble the traumatic event; or bodily reactivity on exposure situations that resemble the traumatic event (DSM-IV-TR, 2000). The person avoids situations that are associated with and remind him or her of the traumatic event, leading to avoidance of thoughts, feelings, or conversations associated with the trauma; activities, places, or people that remind him or her of the traumatic event; an inability to remember details of the event; markedly diminished participation and interest in usual activities; feeling detached and estranged from others; restricted range of emotional expression; sense of a foreshortened future or life span; persistent signs of physiologic arousal, such as difficulty falling asleep or staying asleep, irritability or anger outbursts, difficulty concentrating, excessive vigilance, and exaggerated startle response. These symptoms persist for more than 1 month and cause significant distress and impairment of functioning.

ACUTE STRESS DISORDER

A person is exposed to a traumatic event in which he or she experiences, witnesses, or is confronted by an event or events that involve an actual or perceived threat of death or serious bodily injury, and the person's response involves intense fear, helplessness, or horror. The traumatic event is

continually re-experienced in the following ways: recurrent and intrusive distressing remembrances of the event involving images, thoughts, or perceptions; distressing dreams of the event; acting or believing that the traumatic event is recurring; intense anxiety and distress to exposure to situations that resemble the traumatic event; bodily reactivity on exposure situations that resemble the traumatic event. The person avoids situations that are associated with and remind him or her of the traumatic event, leading to avoidance of thoughts, feelings, or conversations associated with the trauma; activities, places, or people that remind the person of the traumatic event; inability to remember details of the event; markedly diminished participation and interest in usual activities; feeling detached and estranged from others; restricted range of emotional expression; sense of a foreshortened future or life span; persistent signs of physiologic arousal, such as difficulty falling asleep or staying asleep, irritability or anger outbursts, difficulty concentrating, excessive vigilance, and exaggerated startle response. This disorder differs from PTSD in that the symptoms persist for less than 1 month.

SOCIAL PHOBIA (SP)

This disorder is characterized by a persistent and significant fear of one of more social situations in which a person is exposed to unfamiliar persons or scrutiny by others and feels he or she will behave in a way that will be embarrassing or humiliating (DSM-IV-TR, 2000). Exposure to the feared social situations almost always causes significant anxiety, even a panic attack, despite the fact that the anxiety is seen as excessive and unreasonable. This belief may lead to avoidance of such situations or endurance under extreme distress, leading to marked interference in the person's functioning and routine. In children and adolescents, the symptoms must be present for a minimum of 6 months and cause significant impairment in functioning or marked distress in order to warrant the diagnosis. The DSM-III-R diagnosis of avoidant disorder of childhood has been subsumed under this rubric in DSM-IV-TR. Children and adolescents with social phobia usually have few friends and tend to avoid group activity and report feeling lonely. They are also fearful of social situations such as reading aloud in class, asking the teacher for help, eating in the cafeteria, unstructured activities with peers, and so on (DSM-IV-TR, 2000).

SELECTIVE MUTISM

Selective mutism is the failure to speak in social situations when there is no underlying language problem and the child has the capacity to speak (DSM-III-R, 1987). The onset of this disorder is in childhood. The child usually speaks normally in the company of familiar adults or family and familiar settings. At school or in other public settings, the child may be silent. The disorder is considered by some to be a severe form of social phobia as these youth are often painfully shy. The disorder cannot otherwise be explained by a developmental abnormality. There is a high rate of family history of anxiety disorders in these children.

SPECIFIC PHOBIA

This disorder is characterized by persistent and significant fear that is recognized as unreasonable and excessive and that is triggered by the presence or perception of a specific feared situation or object; exposure to this situation or object immediately provokes an anxiety reaction (DSM-IV-TR, 2000). The distress, avoidance, and anxious anticipation of the feared situation or object significantly interfere with a person's normal functioning or routine. This disorder may present as one of many types: the animal type is manifested as a fear of animals or insects; the natural environmental type is manifested as a fear of storms, heights, water, and the like; the blood-injection-injury type is manifested as a fear of getting injections, seeing blood, seeing injuries, or watching or having invasive medical procedures; the situational type is manifested as a fear of elevators, flying, driving, bridges, escalators, trains, tunnels, closets, and so on. In children, specific phobia may be expressed as anxiety or by symptoms such as crying, temper tantrums, or a marked increase in clinging behavior. AQ4

ADJUSTMENT DISORDER WITH ANXIETY (WITH OR WITHOUT DEPRESSED MOOD)

This disorder can be diagnosed when the development of emotional or behavioral symptoms occur within 3 months in response to an identifiable stressor (DSM-III-R, 1987). These symptoms and behaviors cause marked distress in excess of that which could be expected and results in significant occupational, social, or academic performance. Once the initiating stressor has ceased, the disturbance does not last longer than 6 months.

ANXIETY DISORDER DUE TO A GENERAL MEDICAL CONDITION

This disorder may result when the physiologic consequences of a distinct medical condition is judged to be the cause of prominent anxiety symptoms. AQ5

DRUG-INDUCED ANXIETY DISORDER

This disorder may result when the physiologic consequences of the use of a drug or medication is judged to be the cause of prominent anxiety symptoms.

ANXIETY DISORDER NOT OTHERWISE SPECIFIED

This disorder may result when the prominent symptoms of anxiety and avoidance exist but do not fully meet the preceding diagnostic criteria.

DIAGNOSTIC ISSUES IN ANXIETY DISORDERS

As more than 50% of individuals who meet criteria for one anxiety disorder also meet criteria for a second anxiety disorder, an underlying vulnerability to anxiety is probably common to all anxiety disorders (Kashani and Orvaschel, 1990; Last et al., 1992). However, it is not clear whether there is a specific inheritance related to a particular anxiety disorder or whether a broader genetic predisposition toward problems with overarousal and reactivity to stimuli may be responsible. In addition, the categorical DSM-IV-TR nomenclature may result in artificially carving various anxiety disorders into discrete categories.

COMORBIDITY

Childhood anxiety disorders have astounding comorbidity with other childhood neuropsychiatric disorders (Last et al., 1987a; Leckman et al., 1983). Attention-deficit/hyperactivity disorder (ADHD) co-occurs with anxiety disorders with high frequency (Biederman et al., 1991). In some studies, more than 60% of the children with affective disorders also had an anxiety disorder, and 70% of children with school refusal had comorbid affective disorders (Bernstein et al., 1996).

The presence of anxiety disorders in childhood appears to confer risk for the development of affective and anxiety disorders in adolescence and adulthood (Reinherz et al., 1989). In turn, depressive symptoms in childhood apparently play a role in vulnerability to anxiety disorders throughout the life cycle (Kovacs et al., 1989; Kovacs and Goldston, 1991). In addition, adolescents with anxiety disorders who develop major depression are at a high risk for attempting suicide (Pawlak et al., 1999). That many disorders co-occur with anxiety disorders and that vulnerability to anxiety disorders also confers vulnerability to affective disorders, and vice versa, should not be surprising, considering that the brainstem monoamines (e.g., norepinephrine, serotonin, dopamine) are common mediators of both arousal and affect. Primary "anxiety" symptoms induced by abnormal regulation of these brainstem monoamine systems would likely be accompanied by affective symptoms, and vice versa.

Other neuropsychiatric conditions in which anxiety is a prominent symptom include psychotic disorders, mental retardation, traumatic head injury, developmental delay, profound neglect, and physical abuse. The common thread in all of these disorders is a compromised capacity to effectively and efficiently interpret experience. Regardless of which specific capacity (processing, storing, or recalling stored information) is affected by the cortical and subcortical impairments in these disorders, the effect is the same—every experience is too "new." Any condition that alters the brain's capacity to make associations in response to an event, store them, and then generalize from that event to a future event causes the affected individual to experience each moment as novel. Novel cues are interpreted by the brain as threat related until proven otherwise. To a psychotic child in whom abnormal pairing of sensory information is taking place, the environment is ever-changing from moment to moment, with all experience continually being processed and perceived as "novel."

Although anxiety plays a major role in the clinical presentation of all of these neuropsychiatric disorders, no single neuropathological process has been found that is specific to a given diagnostic category or to specific anxiety-related symptoms. The threat-response systems in the human brain are redundant and widely distributed, and there are many mechanisms and sites in which dysregulation may occur.

ANXIETY DISORDER SECONDARY TO NEUROLOGICAL ILLNESS

One of the best described neurological disorders that presents with symptoms of anxiety is pediatric autoimmune neuropsychiatric disorders associated with streptococcal (group A β-hemolytic streptococcal [GABHS]) infections (PANDAS) (Swedo et al., 1998). Swedo et al. described the clinical characteristics of 50 pediatric patients diagnosed with PANDAS, OCD, and tic disorders with a prepubertal onset in association with GABHS. The children's symptom onset was acute and dramatic, typically triggered by GABHS infections at a very early age (mean = 6.3 years, SD = 2.7, for tics; mean = 7.4 years, SD = 2.7, for OCD). The PANDAS clinical course was characterized by a relapsing-remitting symptom pattern with significant psychiatric comorbidity accompanying the exacerbations; emotional lability, separation anxiety, nighttime fears and bedtime rituals, cognitive deficits, oppositional behaviors, and motoric hyperactivity were particularly common. Giedd et al. used computer-assisted morphometric techniques to analyze the cerebral magnetic resonance images of 34 children with PANDAS and 82 healthy comparison children who were matched for age and sex (Giedd et al., 2000). The average sizes of the caudate, putamen, and globus pallidus, but not of the thalamus or total cerebrum, were significantly greater in the group of children with streptococcus-associated OCD or tics than in the healthy children. The basal ganglia enlargements were consistent with a hypothesis of a selective cross-reactive antibody-mediated

inflammation of the basal ganglia underlying the development of poststreptococcal OCD or tics in some individuals. However, there was a lack of correlation between basal ganglia size and symptom severity, indicating that the relationship between basal ganglia size and pathophysiology is not direct. In addition, because of poor sensitivity and specificity of the MRI findings, an MRI scan is not warranted for the diagnosis or clinical monitoring of children with poststreptococcal OCD or tics.

Apart from PANDAS, there are limited descriptions of pediatric anxiety disorders secondary to neurological illness. Gamazo-Garran et al. described a 16-year-old-boy who had a midline germinal tumor affecting the caudate nuclei; left lenticular, right internal capsule's genu; and bilateral involvement of the interventricular septum close to the interventricular foramina. He developed OCD symptoms and elevated tumor markers when he had a tumor relapse, and fluorodeoxyglucose positron emission tomography showed caudate nuclei involvement. He responded to treatment with 80 mg of citalopram. As noted in this case report, the treatment for anxiety secondary to neurological/infectious causes is the same as that for primary anxiety disorders (Storch et al., 2004).

EPIDEMIOLOGY

Although quite common, anxiety disorders in children often are overlooked or misjudged, even though they are treatable conditions with good, persistent medical care. What does seem to be developing in the medical literature is the consensus that many "adult" psychiatric disorders likely have their first (although perhaps subtle or ignored) manifestations in childhood, and that if left untreated these anxiety disorders in children likely progress to adult versions.

Epidemiological studies that used DSM-III-R diagnostic criteria have demonstrated that over 10% of all children meet criteria for some anxiety disorder (Kashani and Orvaschel, 1988; King et al., 1995; Milne et al., 1995). In two cross-sectional epidemiological studies, 21% of the sampled children reported symptoms meeting DSM anxiety disorder diagnostic criteria (Kashani and Orvaschel, 1988; Kashani et al., 1989). In these samples, the prevalence rates for separation anxiety disorder were 12.9%, 12.4% for over anxious disorder, 3.3% for specific phobia, and 1.1% for social phobia. The National Institute of Mental Health (NIMH) adolescent OCD study showed a lifetime prevalence of 1.9% for the general adolescent population (Flament et al., 1988). Valleni-Basile et al. reported a higher rate of 3% of clinical OCD and 19% for subclinical OCD symptoms in their community sample of 3,283 adolescents (Valleni-Basile et al., 1994). A few studies have investigated the epidemiology of panic disorder. These studies have found a lifetime prevalence ranging from 0.3% to 1% in adolescence (Lewinsohn et al., 1993; Verhulst et al., 1997; Whitaker et al., 1990). Warren et al., in a sample of 388 adolescents reported a higher (4.7%) prevalence of panic disorder. Unfortunately, because of controversies regarding the occurrence of panic disorder in the pediatric age group, panic disorder was not mentioned in the most widely cited epidemiological studies of panic disorder in youth (Anderson et al., 1987; Kashani and Orvaschel, 1988)

COURSE

Understanding the course of anxiety disorders is critical to planning treatment and assessing future medical need. In addition, knowledge about the course of various anxiety disorders will answer parental concerns about how long the child will need treatment and when the child might be free from impairment. Emerging evidence is suggesting that several anxiety disorders begin early in childhood, increase the risk for developing other comorbid disorders, and if untreated may result in a chronic course (Achenbach et al., 1995; Pine et al., 1998b; Spence et al., 2001).

Separation anxiety disorder (SAD) can have an early and acute onset following a significant stressor, such as move to a new neighborhood, death of a parent, or a period of developmental change (Last et al., 1987a). SAD tends to have a variable course with remission and periods of recurrence during periods of increased stress and sometimes seems to come out of the blue. Moreover, SAD increases the risk for subsequent depression and social phobia, and girls with SAD are at increased risk for panic disorder and agoraphobia (Black and Robbins, 1990). Simple phobia also seems to be chronic for a significant proportion of children and adolescents, though there have been reports of spontaneous remission also (Agras et al., 1972; Essau et al., 2000).

OCD has a chronic fluctuating course marked by remissions and recurrences (Swedo et al., 1989). In a 2-year follow-up of adolescents who had a lifetime diagnosis of OCD, Berg et al. found that 31% of subjects received a diagnosis of OCD at follow-up (Berg et al., 1989). Wewetzer et al., in a long-term follow-up study, assessed 55 patients whose mean age of onset of OCD was 12.5 years and the mean follow-up time was 11.2 years. At the follow-up investigation, 71% of the patients met the criteria for some form of psychiatric disorder, while 36% were still suffering from OCD.

Patients with social phobia are at increased risk of developing major depression, as well as substance abuse and dependence (Kessler et al., 1994; Last et al., 1992). There are little data available on the course of GAD. However, the minimal data suggest that GAD is unstable over time, with the majority of the patients having a different diagnosis at follow-up in addition to increased risk for alcohol abuse (Cantwell and Baker, 1989; Kaplow et al., 2001). Though data are lacking in children for the course of panic disorder, the data from adults suggests that this is a chronic and recurrent diagnosis (Breier et al., 1986).

Genetic Factors

Systematic study of the temperament of infants has suggested that certain properties of the sensitivity of the arousal system may be constitutional (Kagan et al., 1987). The rudimentary organization and sensitivity of the arousal systems appear to be present at birth. Differential internal states of anxiety seem to be associated with distinct behaviors, such as initiation of social contact, exploration, and the capacity to form and maintain peer attachments (Last et al., 1987b; Waldron et al., 1975). Panic disorder, generalized anxiety disorder, phobias, and OCD all have significant familial aggregation (Hettema et al., 2001). Furthermore, twin studies have established that genes account for a significant variance in anxiety measures. In a large twin study, Torgersen considered 32 monozygotic (MZ) and 53 dizygotic (DZ) adult same-sexed twins (Torgersen, 1983). The frequency of anxiety disorders was twice as high in MZ as in DZ twins of the total proband group, alike in the MZ and DZ co-twins of the generalized anxiety disorder proband group, and three times as high in MZ as in DZ co-twins of the other proband groups. Anxiety disorders with panic attacks were more than five times as frequent in MZ as in DZ co-twins in a combined group of probands with panic disorders and agoraphobia with panic attacks. Thus, for generalized anxiety disorder, heritability was not apparent, while genetic factors seemed significant in other anxiety disorders, especially panic disorder and agoraphobia with panic attacks. Stevenson et al. studied 319 same-gender twin pair and showed that around 29% of the variance for fear and phobic symptoms was heritable (Stevenson et al., 1992).

With advances in molecular genetic techniques and high throughput genotyping methodology (see Chapter ??), scientists have conducted genetic association and linkage studies in an effort to identify specific genes and genetic regions that may increase susceptibility for anxiety disorders.(Please see Table 14.2 for commonly cited genetic studies). Because the animal literature has supported a role for serotonin in anxiety and fear, the usual focus of the studies has been candidate genes that code for neurotransmitters in the serotonin pathway including monoamine oxidase A (MAO-A), catechol-O-methyl-transferase (COMT), serotonin transporter (SLC6A4), receptors involved in serotonin transduction (such as 5HT1B), and GABA-A (Lesch, 2001). As is the case with genetics of complex diseases, findings from linkage and association studies have been inconsistent and conflicting, and therefore need further replication. Thus, several human studies have reported findings of association of polymorphisms in the promoter region of the serotonin transporter gene with anxiety, though other studies have been negative (Battaglia et al., 2005; Katsuragi et al., 1999; Lesch et al., 1996; Nakamura et al., 1997). In association studies of COMT genes in patients with OCD, two studies found an association in males (Karayiorgou et al., 1997, 1999), one found an association for females (Alsobrook et al., 2002a), and another found no association in any gender (Ohara et al., 1998). In one study, Samochowiec et al. looked at association studies of MAO-A, COMT, and serotonin transporter genes polymorphisms in patients with anxiety disorders of the phobic spectrum (Samochowiec et al., 2004). While there were no significant differences between controls (n = 202) and patients (n = 101) in the allele and genotype frequencies of the serotonin and COMT gene polymorphisms, the frequency of >3 repeat alleles of the MAO-A gene polymorphism was significantly higher in female patients suffering from anxiety disorders, specifically panic attacks and generalized anxiety disorder.

AQ6

NEUROBIOLOGY

Overview: Neurobiological Correlates of Anxiety

The prime directive of the human brain is to promote survival and procreation. When potentially threatening cues are present in these environments, the brain activates a complex set of neurophysiological, neuroendocrinological, and neuroimmunological responses to optimize the survival of the individual. In humans, activation of these threat-response systems is accompanied by the subjective perception of anxiety or fear.

An anxiety-inducing or fear-inducing stimulus generates sensory information that is transmitted from the peripheral sensory receptors to the dorsal thalamus. However, sensory information from the olfactory system is not relayed through the thalamus and is relayed to the amygdala and the entorhinal cortex (Turner et al., 1978). Visceral afferent pathways relay information to the amygdala and locus ceruleus directly or through the nucleus paragigantocellularis and nucleus tractus solitarius (Elam et al., 1986; Nauta and Whitlock, 1956; Saper, 1982). The thalamus relays sensory information to the primary sensory receptive areas of the cortex. These primary sensory regions project to adjacent cortical association areas. The visual, auditory and somatosensory cortical association areas send projections to the amygdala, orbitofronatal cotex, entorhinal cortex, cingulate gyrus, and other brain structures.

The hippocampus and amygdala are sites of convergent reciprocal projections form cortical association areas. These interconnections help a single sensory stimulus such as a smell, sight, or sound to elicit a specific memory or flashback along with symptoms of anxiety and fear (in case the smell, sight, or sound was associated with a traumatic event). We examine the possible neurobiological correlates of anxiety disorders in the following section by considering the abnormal organization, regulation, or development of neurobiological systems and subsystems within various brain regions that appear to be involved in sensing, processing, and responding to threat.

TABLE 14.2
GENETIC STUDIES

Candidate Gene	Diagnosis/Trait or Symptom	Results	Reference/Lead Authors
5-HTTLPR (promoter region of the serotonin transporter gene)	Harm avoidance	Association with S allele	(Katsuragi et al., 1999)
	Harm avoidance, neuroticism	Association with S allele	(Lesch et al., 1996)
	Anticipatory worry	Linkage with SLC6A4*C, no association	(Mazzanti et al., 1998)
	Harm avoidance, neuroticism	No association with S allele	(Nakamura et al., 1997)
	Harm avoidance, neuroticism	No association with S allele	(Stoltenberg et al., 2002)
	OCD	No association with S allele	(Cavallini et al., 2002)
	OCD	No association with S allele	(Billett et al., 1997)
	Panic	No association with S allele	(Deckert et al., 1997)
	Panic	No association with S allele	(Hamilton et al., 1999)
	Social phobia	No association with S allele	(Stein et al., 1998)
Catechol-O-methyltransferase (COMT)	GAD	No association with COMT allele	(Ohara et al., 1998)
	OCD	Association with low activity allele, 22q11 microdeletions, Low/Low genotype in males only	(Karayiorgou et al., 1997)
	OCD	Association with low activity allele in males	(Karayiorgou et al., 1999)
	OCD	Association with the low-activity allele in females probands (P = 0.049.	(Alsobrook et al., 2002b)
	OCD	No association with COMT allele	(Ohara et al., 1998)
	Panic	Association with marker D22S944	(Hamilton et al., 2002)
	Panic	No association with COMT allele	(Ohara et al., 1998)
	Phobia	No association with COMT allele	(Ohara et al., 1998)
Monoamine oxidase-A (MOA-A)	OCD	Association with MAO-A*297CGG allele	(Karayiorgou et al., 1999)
HTR1B (Serotonin 1B receptor)	GAD	No association with HTR1B 861G>C polymorphism	(Fehr et al., 2000)
	Panic	No association with HTR1B 861G>C polymorphism	(Fehr et al., 2000)
5HT1Dβ	OCD	No association with a silent G-to-C substitution at nucleotide 861	(Di Bella et al., 2002)

(continued)

TABLE 14.2
(continued)

Candidate Gene	Diagnosis/Trait or Symptom	Results	Reference/Lead Authors
5HTR2A (Serotonin 2A receptor)	Social phobia	No linkage	(Stein et al., 1998)
Genome Wide Scans	Panic	Linkage at 7p15, LOD = 2.2 (469 markers)c	(Crowe et al., 2001)
	Harm avoidance	LOD = 3.2, Linkage with locus on 8p21–23, epistasis with 8p21–23 (291 markers studied)	(Cloninger et al., 1998)
	OCD	LOD = 2.25 on 9p (349 markers studied)	(Hanna et al., 2002)

OCD, obsessive-compulsive disorder; GAD, generalized anxiety disorder.

THREAT-RESPONSE NEUROBIOLOGY IN THE MATURE CENTRAL NERVOUS SYSTEM

Reticular Activating System: Arousal and Alarm

The reticular activating system is a network of ascending, arousal-related neural systems in the brain that consists of locus ceruleus noradrenergic neurons, dorsal raphe serotonergic neurons, cholinergic neurons from the lateral dorsal tegmentum, and mesolimbic and mesocortical dopaminergic neurons, among others. Much of the original research on arousal, fear, and response to stress and threat was conducted using various lesion models of the reticular activating system (Moore and Bloom, 1979). With the advent of more sophisticated neuropharmacological techniques that allowed precise manipulation and lesioning of individual neurochemical systems, the concept of the reticular activating system as a functional unit lost popularity. Recently, however, interest has been rekindled in the reticular activating system as an integrated neurophysiological system involved in arousal, anxiety, and modulation of limbic and cortical processing (Munk et al., 1996). Working together, the brainstem monoamine systems in the reticular activating system provide the flexible and diverse functions necessary to modulate the variety of functions responsible for anxiety regulation.

Locus Coeruleus: Regulation of Arousal

The locus coeruleus is involved in initiating, maintaining, and mobilizing the total body response to threat (Aston-Jones et al., 1986). A bilateral grouping of norepinephrine-containing neurons originating in the pons, the locus coeruleus sends diverse axonal projections to virtually all major brain regions and thus functions as a general regulator of noradrenergic tone and activity (Foote et al., 1983). The locus coeruleus plays a major role in determining the "valence," or value, of incoming sensory information; in response to novel or potentially threatening information, it increases its activity (Abercrombie and Jacobs, 1987a, 1987b). The ventral tegmental nucleus also plays a part in regulating the sympathetic nuclei in the pons/medulla (Moore and Bloom, 1979). Acute stress results in an increase in locus coeruleus and ventral tegmental nucleus activity and the release of catecholamines throughout the brain and the rest of the body. These brainstem catecholamine systems (locus coeruleus and ventral tegmental nucleus) play a critical role in regulating arousal, vigilance, affect, behavioral irritability, locomotion, attention, and sleep, as well as the startle response and the response to stress (Levine et al., 1990; Morilak et al., 1987a, 1987b, 1987c).

A number of other neurotransmitters and neuropeptides play a role in modulating locus coeruleus activity, thus influencing the sensitivity of the threat response. Serotonin (Adell et al., 1988), enkephalins (Abercrombie and Jacobs, 1988), corticotrophin releasing hormone (CRH) (Butler et al., 1990), and epinephrine (Perry et al., 1983; Vantini et al., 1984) all can alter locus coeruleus sensitivity.

Dopaminergic Systems: Sensitization

Dopaminergic systems play a critical role in the response to threat. In animal models, various stress paradigms have demonstrated alterations in dopamine metabolism and dopamine-receptor densities and sensitivity (Kalivas and Duffy, 1989; Kalivas et al., 1988). Dopaminergic systems originating in the mesencephalon send projections to key limbic and cortical areas involved in the afferent and efferent wings of the threat response. These systems are very important in sensation, perception, and interpretation of stress-related and threat-related cues.

Studies of psychostimulant-induced and stress-induced sensitization of dopaminergic systems provide important clues to the neurophysiological mechanisms that may

underlie the development of a sensitized anxiety response (Kalivas et al., 1988). Sensitization—an increased sensitivity to a constant stimulus—occurs in response to specific patterns of activation of these dopaminergic systems. In rats (Kleven et al., 1990), primates (Farfel et al., 1992), and humans (Post et al., 1988), psychostimulants (e.g., methamphetamine, cocaine) administered in moderate dosages can induce dramatic sensitization syndromes that include agitation, impulsivity, autonomic arousal, and even seizures (see case example below). Stress can induce similar sensitization in animal models (Antelman et al., 1980; Kalivas and Duffy, 1989).

CASE EXAMPLE: PSYCHOSTIMULANT-INDUCED PANIC ATTACKS

S., a 16-year-old, was admitted to the emergency room with diaphoresis, tachycardia, a sense of impending doom, and profound anxiety. He had no previous history of psychiatric disorder and denied previous anxiety or panic attacks. S. described a 4-month history of cocaine use characterized by binge nasal use. His last binge was 5 days prior to the admission. Since that time, he had been experiencing an escalating "sensitivity" to stress, with increased irritability and difficulty sleeping. Following an extensive medical and neuropsychiatric workup, S.'s episodes were formulated as reflecting a psychostimulant-induced panic disorder related to a sensitizing pattern of cocaine use. After discharge, S. experienced more panic attacks (approximately two per week) and elected to pursue recommended outpatient treatment. Successful drug rehabilitation and pharmacotherapy with a benzodiazepine anxiolytic for 6 weeks resulted in disappearance of the panic attacks.

Sensitization involves a cascade of cellular and molecular processes that are probably related to long-term potentiation (Brown et al., 1988; Kandel, 1989; Kandel and Schwartz, 1982; Madison et al., 1991). It has been hypothesized that sensitization of the biogenic amines (norepinephrine, epinephrine, and dopamine) in the reticular activating system and related systems plays a key role in the development of seizure disorders (Kalivas et al., 1988), affective disorders (Post, 1992), anxiety disorders (Post et al., 1988), and PTSD in both adults and children.

Organization of the developing brain occurs in a use-
AQ7 dependent fashion (see Chapter ??), and this organization may be affected by hypervigilance or anxiety that is pervasive, out of context, and extreme in reaction to neutral or minor threatening cues (Adell et al., 1988; Konarska et al., 1989). Therefore, many anxiety syndromes may reflect a maladaptive generalized activation of the alarm response (i.e., a sensitization), with symptoms representing exaggerations of originally adaptive and appropriate functions—for example, hypervigilance instead of appropriate prediction and early detection of future danger, and avoidance and reenactment rather than adaptation and survival.

Hypothalamic/Thalamic Nuclei: Sensory Integration

Sensory thalamic areas receive input from various afferent sensory systems, and at this level, "feeling" begins. Although thalamic nuclei are important in the stress response, these regions have been studied primarily as way stations that transmit important arousal information from the reticular activating system neurons (e.g., locus coeruleus noradrenergic neurons) to key limbic, subcortical, and cortical areas involved in sensory integration and perception of threat-related information (Castro-Alamancos and Connors, 1996). The neuroendocrinological—and likely neuroimmunological—afferent and efferent wings of the threat response are mediated by hypothalamic and other anatomically related nuclei. Animal studies have demonstrated important roles for various hypothalamic nuclei and hypothalamic neuropeptides in the stress response (Bartanusz et al., 1993; Miaskowski et al., 1988) (Rosenbaum et al., 1988), and this suggests that future studies in humans may demonstrate a key role of hypothalamic nuclei in anxiety disorders (Young and Lightman, 1992).

Limbic System: Emotion Processing

The central role of the subcortical network of brain structures in emotion was hypothesized by Papez (Papez, 1937). In 1949, MacLean coined the term *limbic system,* a name that integrated Papez's circuit (hypothalamus, anterior thalamus, cingulate gyrus, and hippocampus) with other anatomically and functionally related areas (amygdala, septum, orbitofrontal cortex). Over the years, various regions have been added to or removed from this "emotion"-processing circuit.

Amygdala: Perception of Threat and Emotional Memory

The amygdala has emerged as the key brain region responsible for the processing, interpretation, and integration of emotional functioning (Clugnet and LeDoux, 1990). Just as the locus coeruleus plays the central role in orchestrating arousal, the amygdala plays the central role in the brain in processing afferent and efferent connections related to emotional functioning (LeDoux et al., 1988; Pavlides et al., 1993b; Phillips and LeDoux, 1992b). The amygdala receives input directly from the sensory thalamus, the hippocampus (via multiple projections), the entorhinal cortex, and the sensory association and polymodal sensory association areas of the cortex as well as from various brainstem arousal systems via the reticular activating system (Selden et al., 1991). The amygdala processes and determines the emotional valence of simple sensory input, complex multisensory perceptions, and complex cognitive abstractions, even responding specifically to complex socially relevant stimuli. In turn, the amygdala orchestrates the organism's response to this emotional information by

sending projections to brain areas involved in motor (behavioral), autonomic nervous system, and neuroendocrine areas of the CNS (Davis, 1992a, 1992b; LeDoux et al., 1988). In a series of landmark studies, LeDoux and colleagues demonstrated the key role of the amygdala in "emotional" memory (LeDoux et al., 1990). Animals, including humans, store emotional as well as cognitive information, and the storage of emotional information is critically important in both normal and abnormal regulation of anxiety. The site at which anxiety is perceived is the amygdala (Davis, 1992a). It is in these limbic areas that the patterns of neuronal activity associated with threat—and mediated by the monoamine neurotransmitter systems of the reticular activating system—become an emotion.

Hippocampus: Association, Generalization, and Storage of Threat-Related Cues

A key neuroanatomic region in memory and learning is the hippocampus. This brain area is involved in the storage of various kinds of sensory information and is very sensitive to stress activation (Pavlides et al., 1993a; Phillips and LeDoux, 1992a; Sapolsky et al., 1984). The hippocampus appears to be critical in the storage and recall of cognitive and emotional memory (Selden et al., 1991). Any emotional state related to arousal or threat may alter hippocampal functioning, changing the efficiency and nature of hippocampal storage and retrieval. These state-dependent memory and learning functions are vital for understanding various clinical aspects of childhood anxiety disorders. Threat alters the ability of the hippocampus and connected cortical areas to "store" certain types of cognitive information (e.g., verbal) but does not affect the storage of other types (e.g., nonverbal). Many of the cognitive distortions that appear to be associated with the development of anxiety disorders (e.g., agoraphobia) may be related to anxiety-related alterations in the "tone" of hippocampal and cortical association areas.

Neuronal systems are capable of making remarkably strong associations between paired cues (e.g., the growl of a tiger and threat). Although associations between patterns of neuronal activity and specific sensory stimuli occur in many brain areas, the most complex associations involving the integration of multiple sensory modalities are made in the more complex brain areas (i.e., the amygdala and cortex). Under ideal conditions, this threat-response capacity for association allows rapid identification of threat-related sensory information in the environment, enabling the organism to act quickly to protect its own survival. Yet this remarkable capacity of the brain to generalize from a specific event renders humans vulnerable to the development of false associations and overgeneralizations from specific threat situations to other nonthreatening situations.

In anxiety disorders, specific complex cues (e.g., snakes) may become linked with limbic-mediated emotions (e.g., anxiety). Limbic activation may result from cortically mediated images (e.g., interpreting a specific event as potentially threatening or imagining a specific fear-inducing object such as a snake). Once these limbic areas have been activated, however, it is the sensitivity of the individual's stress-response systems that determines whether the afferent and efferent wings of the alarm response will be activated.

Cortical Systems: Interpretation of Threat

The quality and intensity of any emotional response, including anxiety, depend on subjective interpretation or cognitive appraisal of the specific situation eliciting the response (Maunsell, 1995; Singer, 1995). Most theories addressing the etiology of anxiety disorders focus on the process by which stimuli are "mislabeled" as being "threat" related, thereby inducing a fear response and anxiety in situations where no true threat exists. How individuals "cortically interpret" the limbic-mediated activity (i.e., their internal state) associated with arousal plays a major role in their subjective sense of anxiety (Gorman et al., 1989). Klüver-Bucy syndrome, which results from damage to or surgical ablation of the temporal lobes, is characterized by absence of fear in response to current and previously threatening cues (Kluver and Bucy, 1937). The general disinhibition characteristic of this syndrome suggests a loss of the capacity to recall cortically stored information related to previous threat or to efficiently store threat-related cues from new experience.

Other areas of the cortex play a role in threat. Primary among these are the multimodal association areas, which have direct connections to the amygdala. Important neurotransmitters in cortical as well as other regions involved in threat are gamma-aminobutyric acid (GABA) and glycine. The capacity of benzodiazepines to alter arousal and sensitivity to threat has long been known. Benzodiazepines target the GABA receptor complexes. Although GABA binding sites are ubiquitous in the CNS, the specific brain site at which the benzodiazepines exert their therapeutic effects is unknown. It is likely that the therapeutic effects of these agents are the result of action in multiple areas of the brain, including the cortex.

CASE EXAMPLE: ANXIETY AFTER FRONTAL LOBE DAMAGE

X., an 8-year-old boy, presented to a neuropsychiatric clinic 8 months after a car accident in which he suffered a traumatic head injury. He had sustained significant frontotemporal injury with resulting loss of fluent speech and of motor and complex integrated sensory processing capabilities. Rehabilitative progress was being impeded by symptoms of profound anxiety, unwillingness to travel to the hospital for rehabilitation services, and a combative and "frightened animal"–like reaction when X. was forced to leave the house. All novel situations appeared to trigger his

fearful, regressive, and combative tantrums. Once an episode started, it was nearly impossible to stop, and it took almost a whole day for him to calm down and return to his baseline state.

After extensive neuropsychiatric evaluation, X.'s episodes were conceptualized as being fear equivalents complicated by—and related to—(1) difficulty in processing complex, novel stimuli and (2) failure of previously intact cortical modulatory mechanisms to contain his arousal and impulsivity once they were activated.

Neuropeptides

Hormonal signals affect heterogeneous corticosteroid nuclear receptors—that is, type 1 (mineralocorticoid) or type 2 (glucocorticoid) in the hypothalamic-pituitary-adrenal (HPA) axis. Stressful life events such as isolation increase HPA axis activity (McEwen, 2001). The hippocampus, amygdala, and mPFC are limbic structures that are targets for and also modulate adrenal steroids. Glucocorticoids can result in neurotoxic damage to the hippocampus with suppression of neurogenesis (McEwen, 2001; Sapolsky, 2000). Exposure to stress results in release of corticotrophin releasing hormone (CRH), adrenocorticotrpic hormone (ACTH), and cortisol via activation of the HPA axis. During periods of stress there is partial resistance to feedback inhibition of cortisol release and increase in plasma cortisol levels, in addition to a decrease in glucocorticoid receptors (Sapolsky and Plotsky, 1990). Glucocorticoid receptors are present in the brain in high density in areas relevant to stress and anxiety such as the hypothalamus, hippocampus, serotonergic, and noradrenergic cell bodies on both eneurons and glia. Based on animal studies, mineralocorticoid expression is high in limbic regions such as hippocampus, septum, and amygdala (Reul and de Kloet, 1985; Veldhuis and De Kloet, 1982). Animal studies suggest that stress experienced during critical years of development can have long-lasting effects on HPA axis. For instance, rats that experience in utero stress or early maternal deprivation have increased corticosterone concentrations when exposed to stress. Early postnatal stress is associated with changes in basal concentrations of hypothalamic CRH, mRNA, hippocampal glucocorticoid receptor mRNA, and median eminence CRH, in addition to the stress-induced CRH, cortocosterone, and ACTH release (Levine et al., 1993a, 1993b; Stanton et al., 1988). Adults with PTSD and nonhuman primates with early adverse experiences have elevated CRH concentrations and decreased cortisol levels in the cerebrospinal fluid (Coplan et al., 1996). AQ8

The CRH1 and CRH2 receptors have a reciprocal role in anxiety and stress (Koob and Heinrichs, 1999). While CRH1-deficient mice exhibit diminished anxiety related behaviors, CRH2-deficient mice have heightened anxiety (Bale et al., 2000; Smith et al., 1998; Timpl et al., 1998).

Cholecystokinin (CCK) is an octapeptide that has been implicated in anxiety as well. It is found in high concentrations in the cerebral cortex, amygdala, and hippocampus in mammals (Woodruff et al., 1991). Studies in healthy human subjects suggest that CCK induces anxiety and panic, which can be reduced by lorazepam (de Montigny, 1989). In addition, CCK antagonists seem to have an anxiolytic effect (Bradwejn, 1992).

Neuropeptide Y is another neuropeptide which when administered intraventricularly has anxiolytic effects (Heilig et al., 1989). Thus, disturbance in its regulation may be involved in pathophysiology of anxiety disorders (Heilig et al., 1994).

Perinatal Factors

At birth, infants are capable of exhibiting distress (anxiety) when exposed to loud noises, pain, heights, and strangers (Ball and Tronick, 1971; Bronson, 1972). While it is unwise to presume that what they are feeling is anxiety, it is certainly reasonable to hypothesize that they are experiencing subjective sensations of distress. Distress may be due to feeling cold, having low blood sugar, or hearing loud noises. Any simple set of sensory cues, internal or external, that threatens the integrity of the organism can activate the threat-response apparatus in infants. AQ9

A variety of in utero experiences may influence the sensitivity of the threat-response neurobiology in children. For example, prenatal exposure to psychoactive drugs may disrupt normal development of the brainstem catecholamines (Perry, 1988). In animal models, prenatal and perinatal stress can cause altered development of hippocampal organization and the hypothalamic-pituitary-adrenal axis (Plotsky and Meaney, 1993; Shors et al., 1990).

Whether temperament is related to genetic or to intrauterine factors is unknown. As is true of all complex human behavioral phenomena, it is likely that temperament is the result of a combination of genetic and intrauterine factors and that there is significant individual variation as to which factors are primary.

Developmental Experience

Whereas the brainstem nuclei essential in the reticular activating system and the threat response are intact at birth, thalamic, limbic, and cortical systems are not yet fully developed and organized. The human brain develops sequentially, organizing in a use-dependent fashion and altering neuronal migration, differentiation, synaptogenesis, apoptosis, and other processes of neurophysiological organization in response to a host of external molecular cues (e.g., nerve growth factor, cellular adhesion molecules, pattern, and quantity of neurotransmitter receptor stimulation) (Thoenen, 1995). Therefore, as the child matures, limbic (emotional) and cortical (cognitive) development is very experience sensitive. What is different in the young

child compared with the adult may not be the subjective emotion related to the threat so much as the response of the still-developing CNS to the internal state of distress (Perry and Pollard, 1998) and the capacity of the immature cortex to make complex interpretations of the associations between paired stimuli (Singer, 1995).

Response to Threat

The immature threat-response systems have developmentally appropriate precursors of the mature systems but are quite sensitive to experience. Because the brain organizes and develops in a "use-dependent" manner (Perry and Pollard, 1998), the presence and pattern of threat experienced during childhood play a major role in determining the sensitivity and final organization of the individual's threat-response apparatus. Thus, children who are exposed to traumatic experiences develop anxiety-regulation problems with remarkable consistency (Perry and Pollard, 1998).

The classic adult response to impending threat is fight or flight (Cannon, 1914). Clearly, infants are incapable of effectively fighting or fleeing. Therefore, in response to the same internal state of anxiety and sense of impending doom experienced by the adult, infants will display a different behavior set—they will cry and thrash, and if these are unsuccessful in eliciting a response from the caregiver, they will typically use a very primitive adaptive response comparable to the defeat reaction observed in animals that are subjected to inescapable stress (Henry et al., 1986). When they are extremely anxious, infants and young children typically freeze and may dissociate as opposed to fighting or fleeing (Perry and Pollard, 1998). As children get older, their actions and reactions begin to change (although they may experience the same subjective sensation of anxiety that they did when younger), demonstrating a more "adult-like" efferent wing of the threat response.

Use-Dependent Development

Before developing a mature internal stress-response capacity, the infant has an external stress-response apparatus—the primary caregiver (Bowlby, 1982; Erickson et al., 1985). When feeling internal distress associated with hunger, cold, or fear, the infant cries and the parent responds. If the caregiver responds in a reliable and consistent manner, there occurs over time a "building in" of the neurobiology that allows the infant to carry around, or internalize, what once was an external stress-response capacity (Bowlby, 1969).

Abnormal stress-response capacities and anxiety result when there are anomalies in these early experiences (Lee and Bates, 1985; Schneider-Rosen et al., 1985). These experiences may involve inconsistent or absent soothing by a caretaker or persistent "overmothering"—a situation in which a child's behavior is excessively restricted (allegedly for the child's own protection), such that he or she never has the opportunity to build in and organize (in a use-dependent way) a healthy stress-response apparatus. When such a child reaches school age, he or she has the stress-response apparatus of a much younger child. This mismatch between the developmental maturity of the stress response and the increasing demands of the child's environment can lead to significant school-based anxiety.

As children get older, they develop fears in reaction to specific situations and objects. These fears are common, and some may even involve genetic "fixed-action" patterns developed over eons of evolution (e.g., fear of snakes or of dogs). Most of these specific fears, however, are related to the paired (or mispaired) internalization of cues with anxiety from previous experience. During infancy and childhood, children mirror their caretakers' responses when interpreting internal states of pain, arousal, or anxiety (Ainsworth, 1969; Bowlby, 1969). The child who falls on the playground and hurts her knee will look over to her father to see how to interpret her internal state. She can receive either a calm, reassuring look or an anxious, frightened response. Over time, then, the child will come to label a host of external cues as potentially threatening and certain internal sensations as fearful. This labeling process has been hypothesized to be an etiology of specific phobias and generalized anxiety disorders in children. Another illustration of these principles is seen in the offspring of adults with PTSD; such children often develop PTSD-like symptoms in response to the same cues that trigger PTSD symptoms in their parents.

CLINICAL IMPLICATIONS

Conceptualizing Anxiety as Related to the Neurobiology of Threat

Diverse areas of brain appear to be involved in the response to threat. For example, the subjective symptom of anxiety may result from either cortically originated signals (e.g., a thought) or brainstem-originated signals (e.g., tachycardia, hypoxia). In each of these situations, a different primary pathophysiology can produce the same subjective sense of anxiety. The specific phenomenology and treatment issues associated with anxiety disorders and anxiety symptoms in other neuropsychiatric disorders reflect this diverse pathophysiology. The current classifications of childhood anxiety disorders depend on the phenotypic manifestations of emotional and behavioral functioning. Similar phenotypic manifestations, however, are likely to result from a variety of etiologies. The anxiety that manifests as the predominant symptom in any given disorder may be related to dysregulation within any of the key threat-response systems previously described or any combination of these systems. In addition, the principal "deficit" in any given system (e.g., locus coeruleus) may be attributable to dysfunction within any single neurobiological process or combination of processes (e.g., altered adrenergic receptor/effector coupling, abnormal neurotransmitter reuptake or release, inefficiencies in membrane transduction). Clearly, complex neurobiology underlies anxiety regulation.

ASSESSMENT AND TREATMENT

The assessment of anxiety in children and adolescents is based on a thorough neuropsychiatric history and examination. Semistructured interviews are usually used in research settings for diagnosis such as the Anxiety Disorders Interview for Children (Silverman and Nelles, 1988), the Schedule for Affective Disorder and Schizophrenia for School-Age Children (K-SADS) (Kaufman et al., 1997), and the Diagnostic Interview for Children and Adolescents (Welner et al., 1987). A thorough diagnostic interview is usually sufficient in a clinical setting to confirm a diagnosis of anxiety disorders. Anxiety disorders should be considered in cases (even though anxiety may not be the primary complaint) with recurrent complaints of gastrointestinal symptoms, headaches, especially if these tend to resolve on weekends or vacations and present in anticipation of an anxiety-provoking stimulus. Frequent primary care visits for a variety of somatic complaints could also be a manifestation of anxiety disorders (Beidel et al., 1991). Inattentiveness in school could be secondary to anxiety, as anxious children can be preoccupied with anxiety provoking cognitions and appear distractible. It is also important to evaluate the intensity of symptoms, whether they cause functional impairment and evaluate their existence in a number of different contexts such as school or social gatherings. In addition, it is important to take a good history of concomitant medications as some medications may induce anxiety symptoms, such as St. John's wort, ephedra preparations, caffeine containing preparations, sympathomimetics, and asthma medicines.

A family history of anxiety disorders can assist with clinical diagnosis. In addition, it is helpful to ascertain the family history of response to treatment interventions as this has the potential to inform treatment.

Children often are not good historians; therefore, it is important to interview caregivers separately in addition to interviewing the patient in a developmentally sensitive manner. Young children can convey with gestures whether anxiety is a great big problem or a little problem. Older children can use a scale of 0 to 10 with 0 being never worried and 10 being intense fear or worry about many things. Children respond well to questions asking whether they worry or are fearful of things more than other kids. Children and parental ratings of each symptom (on a scale of 1 to 10) and examples of functional impairment (hours of rituals, missing school, avoidance of parties) can be written down at each visit to monitor progress. Patient rated, subjective scales such as the Supervised Children Manifest Anxiety Scale (Reynolds and Richmond, 1997) and the Multi-Dimensional Anxiety Scale (MASC) (March et al., 1997) can also be used to monitor progress. Clinician rated instruments that have utility in clinical and research settings include the Hamilton Anxiety Rating Scale (HAM-A)(Hamilton, 1959), the Children's Yale Brown Obsessive Compulsive Scale (CY-BOCS) (Scahill et al., 1997), and the Screen for Child Anxiety Related Emotional Disorders (SCARED) (Birmaher et al., 1999).

Laboratory studies are obtained only if indicated by the history or examination. Thyroid screening (thyroid stimulating hormone levels) should be considered, unless anxiety symptoms are clearly contextual, such as in specific phobia or social phobia. Neuroimaging studies are not used for diagnostics because of poor sensitivity and specificity in anxiety disorders.

Among the most effective treatments of childhood anxiety disorders are cognitive-behavioral interventions (CBT) (Compton et al., 2004; Pediatric OCD Treatment Study (POTS) Team, 2004). CBT includes a diverse collection of complex interventions including cognitive restructuring and exposure-based interventions that promote habituation or extinction of inappropriate fears (Graziano et al., 1979). CBT also emphasizes psychodeducation as it can enhance compliance, family participation, and treatment success. Information resources for families are provided in Table 14.3. CBT also fits well into the current medical practice environment that encourages and values empirically supported, brief, problem-focused treatments.

The practice parameters for the assessment and treatment of pediatric anxiety disorders developed by the American academy of child and adolescent psychiatry recommend that pharmacotherapy should not be used as the sole intervention but as an adjunct to behavioral or psychotherapeutic interventions (Bernstein and Shaw, 1997). This is because of persuasive empirical support for CBT and the belief that benefits from CBT may be more enduring than pharmacotherapy (Bernstein and Shaw, 1997). Though these parameters were published in 1997, this treatment approach has been supported by subsequent comparative research where CBT appears at least as effective as pharmacotherapy (Pediatric OCD Treatment Study (POTS) Team, 2004). In addition, concerns about safety of antidepressants make CBT the first-line intervention (Newman, 2004). Utilization of pharmacotherapy is recommended when there is inadequate improvement with CBT (Bernstein and Shaw, 1997).

Although, data supporting the efficacy of anxiolytic pharmacotherapy in children are limited, progress has been made with publication of large multisite controlled trials using selective serotonin reuptake inhibitors (SSRIs). SSRIs are the first-line pharmacological interventions for pediatric anxiety disorders. Table 14.4 presents an overview of SSRIs.

The first large pediatric OCD trial utilized fluvoxamine, an SSRI, in a controlled trial of 120 subjects, ages 8 to 17 years (Riddle et al., 2001). This double-blind, placebo-controlled study utilized 10 weeks of core treatment, followed by a 1-year extension phase. The average daily dose of fluvoxamine was approximately 150 mg/d, and the dose range was between 50 and 200 mg/d. Significant improvement of OCD symptoms began at week 1 and continued over the course of the study. Improvement was

TABLE 14.3
RESOURCES FOR FAMILIES AND PATIENTS

Books

Helping Your Anxious Child: A Step-by-Step Guide for Parents by Ronald M. Rapee (Editor), New Harbinger Publications
Your Anxious Child: How Parents and Teachers Can Relieve Anxiety in Children by John S. Dacey, Lisa B. Fiore, Jossey-Bass
The OCD Workbook: Your Guide to Breaking Free From Obsessive-Compulsive Disorder by Bruce M. Hyman PhD, Cherry Pedrick RN, New Harbinger Publications
Freeing Your Child from Obsessive-Compulsive Disorder : A Powerful, Practical Program for Parents of Children and Adolescents by Tamar E. Chansky, Three Rivers Press

Support Organizations and Their Web Sites

www.ocfoundation.org (Obsessive Compulsive Foundation)
www.nimh.nih.gov/publicat/anxiety.cfm (National Institute of Mental Health)
www.athealth.com/consumer/newsletter (Ahealth.com is a provider of Mental Health Information)
www.nmha.org/children (National Mental Health Association)
www.nami.org (National Alliance for the Mentally Ill)
www.adaa.org (Anxiety Disorders Association of America)

noted on three outcome measures: the Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS), the National Institute of Mental Health Obsessive-Compulsive Scale (NIMH-OCS), and the Clinical Global Impressions-Improvement Scale (CGI). Fluvoxamine was well tolerated and few subjects dropped out due to lack of efficacy (9%) or untoward effects (3%). These data resulted in an FDA indication for fluvoxamine for treatment of OCD in children and adolescents ages 8 to 17 years old. This trial was followed by another large controlled SSRI trial for OCD was a sertraline study of 187 children and adolescents, ages 6 to 17 years old (March et al., 1998). Patients were treated with sertraline during a 4-week titration up to 200 mg/d, followed by 8 weeks at a stable dose. Significant differences between sertraline and placebo emerged at week 3 and persisted for the duration of the study. In intent-to-treat analyses, patients treated with sertraline showed significantly greater improvement than did placebo-treated patients on the CY-BOCS (adjusted mean, −6.8 versus −3.4, respectively; P = .005), the NIMH OCS (−2.2 versus −1.3, respectively; P = .02), and the CGI-I (2.7 versus 3.3, respectively; P = .002) scales. Significant differences in efficacy between sertraline and placebo emerged as early as 3 weeks and persisted for the duration of the study. These data earned an Federal Drug Administration (FDA) indication for sertraline treatment of OCD in children and adolescents ages 6 to 17 years old. This study was followed up by a randomized controlled trial of sertraline, cognitive behavioral psychotherapy (CBT), and a combination of CBT and sertraline in 112 children and adolescents diagnosed with OCD (Pediatric OCD Treatment Study [POTS] Team, 2004). Intent-to-treat random regression analyses indicated a statistically significant advantage for sertraline alone (P = .007),and combined treatment (P = .001) compared with placebo. Combined treatment also proved superior to CBT alone (P = .008) and to sertraline alone (P = .006), which did not differ from each other. The rate of clinical remission for combined treatment was 53.6% (95% confidence interval [CI], 36% to 0%); and for sertraline alone. AQ10

TABLE 14.4
SELECTIVE SEROTONIN REUPTAKE INHIBITORS

Agent	FDA Pediatric Labeling	Clinical Use	Dose-Mg/d	Schedule	Adverse Effects
Fluoxetine	OCD (7–17 years)	OCD, GAD, SP, SAD, PD	5–60	QD	Suicidality, irritability, insomnia akathesia, GI disturbance
Paroxetine	N/A		10–30	QD	Headache
Sertraline	>6 years for OCD		25–200	QD	Rash, fluelike symptoms on rapid discontinuation, CYP inhibition
Fluvoxamine	>8 years for OCD		12.5–200	QD	
Citalopram	N/A		10–40	QD	
Escitalopram	N/A		5–30	QD	

OCD, obsessive-compulsive disorder; GAD, generalized anxiety disorder; SP, social phobia; PD, panic disorder.

Rosenberg et al. utilized paroxetine (10 to 20 mg) in a 12-week, open-label trial with 20 patients diagnosed with OCD, ages 8 to 17 years. Paroxetine was effective in this small sample as mean CY-BOCS scores decreased significantly ($z = 3.49$, $p = .0005$) from 30.6 +/− 3.5 to 21.6 +/− 6.8. Another psychotropic agent with controlled safety and efficacy data for pediatric OCD is clomipramine (DeVeaugh-Geiss et al., 1992; Flament et al., 1985; Leonard et al., 1989), a tricyclic antidepressant with potent serotonin (5-HT) reuptake inhibitor and noradrenergic activity. DeVeaugh-Geiss et al. enrolled 60 children, ages 10 to 17 years old and diagnosed with OCD, and demonstrated significant improvements in OCD symptoms (DeVeaugh-Geiss et al., 1992). The side effects from clomipramine were those seen typically with tricyclic antidepressant such as tachycardia, decreased systolic blood pressure, dry mouth, somnolence, dizziness, fatigue, tremor, and constipation. In a meta-analysis, Geller et al. demonstrated that clomipramine was statistically superior to SSRIs in reducing OCD symptoms but did not recommend it as a first-line treatment due to its side effect profile (Geller et al., 2003). The SSRIs examined in this meta-analysis had equivalent efficacy in this population (Geller et al., 2003).

Data are also emerging on the efficacy of SSRIs in anxiety disorders such as social phobia (SP), separation anxiety disorder (SAD), and generalized anxiety disorder (GAD). However, no pharmaceutical agent is currently approved by the FDA for treatment of these disorders in children and adolescents. The Research Unit on Pediatric Psychopharmacology Anxiety Study Group (RUPP, 2001) studied 128 children who were 6 to 17 years of age; who met the criteria for social phobia, separation anxiety disorder, or generalized anxiety disorder; and who had received psychological treatment for three weeks without improvement. The children were randomly assigned to receive fluvoxamine (at a maximum of 300 mg per day) or placebo for 8 weeks. Subjects in the fluvoxamine group had a mean (+/−SD) decrease of 9.7+/−6.9 points in symptoms of anxiety on the Pediatric Anxiety Rating Scale (range of possible scores, 0 to 25, with higher scores indicating greater anxiety), as compared with a decrease of 3.1+/−4.8 points among children in the placebo group ($P \leq 0.001$). On the Clinical Global Impressions-Improvement scale, 48 of 63 children in the fluvoxamine group (76%) responded to the treatment, as indicated by a score of less than 4, as compared with 19 of 65 children in the placebo group (29%, $P \leq 0.001$)(RUPP, 2001).

Birmaher et al. evaluated the efficacy of fluoxetine for the acute treatment of pediatric GAD, SAD, or SP by randomizing youths (7 to 17 years old) who had significant functional impairment due to the above diagnoses to fluoxetine (20 mg/day) ($n = 37$) or placebo ($n = 37$) for 12 weeks (Birmaher et al., 2003). Using intent-to-treat analysis, 61% of patients taking fluoxetine and 35% taking placebo showed much to very much improvement. Youths with social phobia and generalized anxiety disorder responded better to fluoxetine than placebo, but only social phobia moderated the clinical and functional response. Severity of the anxiety at intake and positive family history for anxiety was a predictor of poorer functioning at the end of the study (Birmaher et al., 2003).

In a multicenter, 16-week, randomized, double-blind, placebo-controlled trial with flexible-dose paroxetine, Wagner et al. enrolled 322 children (8 to 11 years of age) and adolescents (12 to 17 years of age) with social anxiety disorder as their predominant psychiatric illness (Wagner et al., 2004). Patients were randomized to receive paroxetine (10 to 50 mg/d) or placebo. At the week 16 last observation carried forward end point, the odds of responding (Clinical Global Impression-Improvement score of 1 or 2) were statistically significantly greater for paroxetine (77.6% response than for placebo 38.3% response [59/154]) (adjusted odds ratio, 7.02; 95% confidence interval, 4.07 to 12.11; $P \leq 001$). The proportion of patients who were "very much" improved (Clinical Global Impression-Improvement score of 1) was 47.8% (77/161) for paroxetine compared with 14.9% (23/154) for placebo.

Based on these data, SSRIs are a useful intervention for pediatric anxiety disorder. While prescribing SSRIs, it would be prudent to weigh the risks against the benefits of prescribing these agents. SSRIs may produce stomachache, nausea, vomiting, diarrhea, and anorexia (Birmaher et al., 2003; Scharko, 2004). According to a joint advisory committee for the Food and Drug Administration, antidepressants can increase the risk of suicidal behavior in the pediatric age group. On September 14, 2004, the advisory committee voted in favor of a "black box warning" stating the risk of suicidality with antidepressants in acute treatment trials. This warning was based on a pooled analysis of short-term (4 to 16 weeks) placebo-controlled trials of nine antidepressant drugs (SSRIs and others) in children and adolescents with MDD and other anxiety disorders including OCD. This analysis included 24 trials with approximately 4,400 patients, and it revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) across all antidepressants and almost all trials during the first few months of treatment in those receiving antidepressants. The average risk of such events on drug was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

FUTURE DIRECTIONS

The completion of a working draft of the human genome sequence promises to provide unprecedented opportunities to explore the genetic basis of individual differences in anxiety disorders, in addition to vulnerability to fear and anxiety (Hariri and Weinberger, 2003). Functional neuroimaging, because of its unique ability to assay information processing at the level of brain, will be a powerful approach that will supplement functional genomics.

Published fMRI studies are already beginning to established important physiological links between functional genetic polymorphisms and differences in information processing within specific brain regions (Hariri et al., 2005). Further utilization of such technical advancements is likely to improve understanding of the biological basis of anxiety disorders, which could lead to novel and more effective treatments for these disorders. Since the mid-1990s, results of several large clinical trials have been published or presented in scientific conferences. These trials demonstrate that often the best available treatments fail to produce full symptom remission. Therefore advancement in scientific knowledge is sorely needed to aid development of new and better treatments.

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AUTHOR'S QUERIES

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