Neurobiology of Early-onset Anxiety Disorders

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The past two decades of research on both the longitudinal course and familial distribution of anxiety disorders suggest that many forms of adult anxiety disorders can be conceptualized as developmental conditions. Family studies demonstrate strong associations between anxiety in parents and children (Battaglia et al. 1998; Weissman et al. 1997). Similarly, prospective epidemiological studies find strong associations between anxiety during adolescence and anxiety, as well as major depression, during adulthood (Pine 1999). Given the lifelong implications of anxiety disorders in childhood and adolescence, it is critical to understand the basic neurobiological mechanisms involved in these disorders early in their developmental trajectory.

Clinical characteristics of childhood anxiety disorders have made them particularly challenging to study, highlighting the importance of using neurobiological markers to eventually improve the nosological system and to develop targeted interventions. For example, childhood anxiety disorders exhibit high rates of comorbidity in both community- and clinic-based studies (Gurley et al. 1996; Verduin & Kendall 2003). Comorbidity appears particularly high for generalized anxiety disorder (GAD) in children, which shows strong associations with a range of conditions, including social anxiety disorder (SAD) and major depression (Kessler & Walters 1998; Pine 1999). Such high rates of comorbidity raise questions as to the validity of current nosological categories and suggest the need for alternative bodies of knowledge to validate conditions (Pine 2007). Additionally, there is an apparent contradiction between the transient nature of some childhood anxiety disorders and evidence suggesting that adult mood and anxiety disorders often begin in childhood. Longitudinal data suggest that this paradox may result from very high rates of childhood anxiety disorders. In most children, these disorders remit. However, those children who remain anxious may account for a large proportion of adult cases of both mood and anxiety disorders. Given this possibility, there is a pressing need to determine factors that distinguish anxious children at low versus high risk for continued anxiety or depression in adulthood. With advances in neurobiological understandings, new avenues for developing such insights are available. Specifically, children and adolescents who manifest clinically significant anxiety but then mature to become adults free of such anxiety might be viewed as having successfully extinguished their fears. Anxious children and adolescents who remain anxious as adults can be viewed as suffering from a deficiency in extinction (Pine et al. 2009). Monumental increases have occurred in understandings of fear extinction neurobiology. As such, the view of persistently anxious children as suffering from some form of “extinction deficit” generates novel insights for treatments that target anxiety by attempting to facilitate extinction.

The current chapter reviews the progress that has been made in the development of neurobiological models of pediatric anxiety disorders, as well as ongoing efforts to bridge basic science and clinical research. The first section briefly reviews the clinical characteristics of pediatric anxiety disorders. Post-traumatic stress disorder and obsessive-compulsive disorder will not be covered in the present chapter and can be found in Chapters X and Y. The second section reviews the basic science research of the neurobiology of fear responses that has provided the foundation for studies of youth with clinical anxiety. The third section will survey clinical research on the neurobiology of anxiety disorders in children and adolescents. Specific physiological responses associated with fear and panic, as well as genetic influences on clinical symptoms associated with anxiety disorders, will also be presented. The concluding section presents future directions for research on...
the neurobiology of anxiety disorders, with a focus on
developmental approaches.

ANXIETY DISORDERS: SYMPTOMS
AND PREVALENCE

Anxiety disorders are the most commonly occurring
psychiatric conditions affecting children and adoles-
cents. Although the prevalence of anxiety disorders
varies by the manner in which they are operationalized
and assessed, estimates range from 3% to 30% for youth
under the age of 18 (Costello et al. 2005). Despite the
fact that some children with anxiety disorders are effec-
tively treated with empirically based treatment (e.g.,
exposure therapy for specific phobia) or experience a
reduction in symptoms as they mature (e.g., SAD), even
children with remitted anxiety remain vulnerable for
later-life recurrences. Approximately 50% of children
with anxiety disorders have some type of psychopathol-
ogy in adulthood (Copeland et al. 2009; Gregory 2007;
Pine et al. 1998). Therefore, significant gaps remain in
the effective lifelong management of these disorders.

Fear is a normal response to danger or threat.
Additionally, some fears are normative at certain devel-
opmental stages (i.e., separation anxiety in toddlers,
social anxiety in adolescents). This presents a challenge
to clinicians and researchers working with fearful
youth. Broadly conceptualized, anxiety disorders occur
when an individual experiences clinically excessive fear,
either in the absence of a real threat or out of propor-
tion to the threat, and this fear causes significant func-
tional impairment in any one of various domains. This
impairment in functioning is usually related to avoiding
situations that will elicit fear or that are perceived as
threatening. For example, a child with social phobia
who fears rejection or embarrassment in social situa-
tions may avoid these situations and instead surround
himself with individuals who will not reject him (e.g.,
parents, siblings). The following sections review the
symptoms and prevalence of the five most common
anxiety disorders in childhood: GAD, SAD, panic dis-
order, social phobia, and specific phobia.

Generalized Anxiety Disorder

According to the Diagnostic and Statistical Manual of
Mental Disorders, Fourth Edition (DSM-IV), GAD
occurs when worry becomes pervasive in daily func-
tioning. Individuals with GAD worry about a range of
situations, including but not limited to those focused on
approval, competence, future events, and new or unfa-
miliar situations. Before 1994, with the publication of
DSM-IV, children presenting with symptoms of perva-
sive worry typically were classified as suffering from
overanxious disorder (OAD), a condition that appeared
in both DSM-III and DSM-III-R. With the 1994 publi-
cation of DSM-IV, the diagnosis of OAD was elimi-
nated, and children presenting with pervasive worry
were classified as suffering from GAD. Questions do
remain about the advantages and disadvantages of this
revision. On the one hand, there may be subtle differ-
ences in the longitudinal outcomes of children in
the community presenting with OAD or GAD-typical
symptoms, leading some to suggest that OAD and GAD
are different conditions (Copeland et al. 2009). On the
other hand, the overwhelming majority of children seen
in the clinic with symptoms of either disorder meet cri-
teria for both. As such, diagnosing such children with
GAD utilizes a diagnostic approach consistent with that
used among adults, thereby encouraging attempts to
relate anxiety across the lifespan.

Children with GAD often seek reassurance to help
allay fear, although this reassurance is typically ineffec-
tive. Somatic complaints and irritability are also char-
acteristic of GAD. In terms of comorbidity, GAD or
OAD in childhood is closely linked with other anxiety
disorders, as well as to depression, and may hold simi-
lar genetic predispositions (Lau & Pine 2008; Pine
1999). This relationship may represent the broad frac-
tures in social and emotional functioning common to
both GAD and major depressive disorder.

The symptoms of GAD in youth are often difficult to
differentiate from those of other anxiety disorders, such
as social phobia and separation anxiety disorder. This
difficulty of differential diagnosis is related to the fact
that the type of pervasive worry found in children with
GAD often centers around issues related to social inter-
action and academic performance, which can closely
mirror these other disorders. For example, a child may
worry about doing well at school, and it may be diffi-
cult to determine if the pervasiveness of the worry meets
criteria for GAD or if it is better captured by socially
phobic fears of evaluation. Additionally, these overlap-
ning symptoms likely contribute to the significant
comorbidity of GAD with other anxiety disorders. As a
result, most studies of pediatric GAD include heteroge-
nous samples with significant comorbidity precluding
specific conclusions about GAD.

High risk for adult psychopathology associated with
childhood GAD has been demonstrated, although, as
noted above, some questions do remain on the degree
to which early risk is best exemplified by children with
OAD as opposed to GAD (Copeland et al. 2009; Pine
et al. 1998). Both retrospective and prospective data sug-
gest that adolescent GAD strongly predicts adult major
depression (Kessler & Walters 1998; Pine 1999). These
data are consistent with data from family studies on the
associations between childhood GAD or OAD and adult
major depression (Copeland et al. 2009; Pine 1999).
These associations may partially arise through the effects
of stress, as adverse life events during adolescence show
the strongest and most consistent association with depression and GAD (Pine 2003).

Separation Anxiety Disorder

Separation anxiety disorder is characterized by an extreme fear of separation from the home or from an attachment figure (e.g., parent). Symptoms must begin before age 18, persist for at least 4 weeks, and be beyond what is expected for the individual’s developmental level. As a result, it is the only anxiety disorder that is classified as a disorder first diagnosed in childhood in the DSM-IV. Separation anxiety disorder typically develops during middle childhood. Rates of the disorder show a relatively marked decline from childhood to adolescence, consistent with age-related changes in the related normal developmental phenomenon of separation anxiety. These data raise questions about factors that distinguish normal from pathological separation anxiety. Findings from longitudinal studies reveal a relationship between SAD and later panic attacks (Pine 1999). Moreover, family studies find that childhood separation anxiety disorder relates to adult panic disorder (Battaglia et al. 1998; Capps et al. 1996; Warner et al. 1995; Weissman et al. 1997). Other data suggest high rates of separation anxiety disorder in children of parents with other psychiatric disorders, such as major depression (Biederman et al. 2001).

Panic Disorder

Panic disorder is characterized by the presence of recurrent, unexpected panic attacks followed by at least 1 month of significant worry about the recurrence or consequences of another panic attack, as well as behavioral changes involving avoidance of triggers associated with panic attacks. Panic disorder is further qualified as occurring either in the presence or absence of agoraphobia, the fear of places or situations in which escape might be difficult or where embarrassment is likely if a panic attack were to occur. Panic attacks are a period of intense discomfort or fear that is accompanied by at least four somatic or cognitive symptoms such as nausea, chest pain, fear of dying, or chills. Panic attacks can be unexpected, situationally bound, or situationally predisposed, and each of these types is defined by a different set of relationships between the panic attack and the trigger. Panic disorder is very rare before adolescence (Costello et al. 1996), exhibiting rates that are generally below 1% for lifetime diagnosis (Pine 1999). In general, children tend to exhibit a relatively abrupt increase in rates of panic attacks around puberty (Hayward et al. 1992), although such panic attacks only infrequently progress to full-blown panic disorder (Pine 1999). In these children, panic attacks typically progress to panic disorder over a relatively lengthy period, into early adulthood.

Social Phobia

The terms social phobia or social anxiety disorder refer to a pattern of recurrent fear and apprehension in social situations or scenarios in which an individual believes he or she may be scrutinized. Individuals with social phobia experience an immediate fear response, and may even have a panic attack, when exposed to social or evaluative situations. Social situations are typically avoided or endured with distress, and this must cause functional impairment. Although adults and adolescents with this disorder often acknowledge that their fear is excessive, this is not typically the case with children. For individuals under the age of 18, symptoms must persist for at least 6 months before a diagnosis of social phobia can be made. Available data from epidemiological studies suggest that social phobia represents a relatively common primary diagnosis among adolescents (Pine 1999; Stein et al. 2000; Velting & Albano 2001; Wittchen et al. 2000).

Pediatric rates of social phobia peak in adolescence, mirroring normal developmental increases in social anxiety (Pine 1999; Stein et al. 2000). This raises questions about factors that distinguish adolescents with “normal” as opposed to “pathological” aspects of social anxiety. Specifically, the presence of moderate social anxiety may be viewed as developmentally appropriate and within the range of normal adaptive behavior, particularly during adolescence. For a sizable minority of children and adolescents, however, social anxiety becomes maladaptive, causing significant distress and impairment.

Early signs of potential risk for social phobia may be manifested in a temperamental profile, namely behavioral inhibition, recognizable early in life. This profile refers to a pattern of wariness in novel situations, particularly new social situations. Although children with behavioral inhibition face a high risk for various childhood anxiety disorders, by adolescence this risk is specific for social phobia (Schwartz et al. 1999). There is also evidence for a common neurobiological substrate underlying behavioral inhibition and social anxiety (Perez-Edgar et al. 2007).

Specific Phobia

Specific phobia refers to an unreasonable fear of a specific object or environmental condition that causes impairment in normal functioning, primarily due to avoidance of feared situations or objects. Diagnosis is appropriate only if the avoidance or fear interferes with functioning or if the fear is felt to be clinically significant in terms of overall magnitude. For diagnosis before
the age of 18, symptoms must persist for more than
6 months. Typical onset occurs during childhood,
although it may arise in other developmental periods.
As with social phobias, adults and adolescents with spe-
cific phobias typically realize that their fear is excessive,
whereas children often do not. Data on developmental
changes in phobias, as abnormal conditions, show par-
allels with data on developmental changes in normal
specific fears, such as childhood fears of small animals
or the dark. Prevalence of specific phobia in children
and adolescents has been estimated at approximately
3%–4%, with the highest prevalence generally appear-
ing between 10 and 13 years of age (Essau et al. 2000;
Fyer et al. 1998).
Specific phobias in children generally cluster into
three subtypes, similar to those found in adults. Children
7–19 years of age report animal phobias, blood injec-
tion–injury phobias, and environmental-situational
phobias (Muris et al. 1999). Of these three subtypes,
20 blood phobia has been shown to result in physiological
symptomatology consisting of an initial rise in heart
rate, followed by vasovagal bradycardia and, frequently,
syncope (Marks 1988). This may indicate a uniquely
23 different neurobiological substrate of blood/injection/
24 injury phobia relative to other specific phobias.

NEUROBIOLOGY OF FEAR

Basic science research has provided a critical founda-
tion upon which biological studies of anxiety disorders
are based. Pioneering research by basic scientists such
30 as Joseph LeDoux and Michael Davis provides essential
evidence that the amygdala is a vital brain region for
32 quickly processing threatening stimuli across species
(Davis 1988; LeDoux 2000). The amygdala and related
brain systems, including but not limited to the prefrontal
cortex, are also central to effective functioning in
threat perception, social response, and emotion pro-
cessing (Phelps & LeDoux 2005; Pine 2003, 2007). These findings have raised
questions about the impact of anxiety disorders on
amygdala and prefrontal cortex development during adolescence, when key social-cognitive processes are
forming.

The amygdala’s role in fear responding has been fur-
37 ther examined using socially salient stimuli such as
38 faces. Early work in this area revealed that adults with
39 bilateral amygdala damage have impaired recognition
of fear expressions (Adolphs et al. 1995). Imaging
40 studies of adults have shown amygdala activation in
response to angry faces (Easter et al. 2005) representing
direct threat, and fearful faces, which represent an
44 ambiguous or unknown threat (Whalen et al. 1998).
Similarly, amygdala activation during the viewing of
46 fearful faces compared to control stimuli has been dem-
47 onstrated in studies of children and adolescents (Guyer
et al. 2008). Moreover, there is some evidence of dif-
erential amygdala sensitivity to fearful faces across
development, although the directions of the findings, in
terms of greater activation among younger relative to
older individuals, varies with methodological aspects of
the studies (Guyer et al. 2008). These findings, along
49 with data showing age-related changes in face-emotion
processing (Thomas et al. 2007), suggest development-
50 al shifts in amygdala-based circuits that may contrib-
51 ute to the development of anxiety disorders in youth.

CLINICAL RESEARCH FINDINGS

Neuroimaging

Similarities in the neurobiological correlates of fear
responses in rodents, nonhuman primates, and humans
implicate particular neural circuits in the pathophysiology of anxiety disorders (Pine 2007). However, even with advances in functional magnetic resonance imaging (fMRI) research, efforts to link clinical symptoms with neural circuits are still in preliminary stages, particularly for children and adolescents. These developmental periods carry several challenges, including rapid neurobiological changes as well as the fact that nosology is often based upon adult presentation of disorders. Given these challenges, researchers have focused on neural circuits associated with known cognitive processes pertaining to fear in animals to establish a neural basis for anxiety disorder symptoms. This extensive body of research implicates the amygdala in fear processing across species. In adults, patients with various anxiety disorders, particularly social phobia, show greater amygdala activity in response to feared or emotional stimuli than do nonanxious controls (see Etkin & Wager 2007, for a meta-analytic review). Similar results have been observed in pediatric samples and are summarized in Table 10.1. For example, functional neuroimaging studies demonstrate an increased amygdala response to negative face-emotion displays in pediatric anxiety disorders (McClure et al. 2007; Monk et al. 2008). Recent evidence suggests that amygdala hyper-reactivity to feared stimuli may underlie cognitive biases observed in children and adolescents with anxiety disorders. For example, youth with anxiety disorders show more activation in the amygdala than do nonanxious youth when they direct their attention to their internally experienced levels of fear (McClure et al. 2007). Additionally, the degree of amygdala activation has been found to correlate with the severity of anxiety symptoms and the degree of attentional biases toward a social threat (e.g., an angry face) (Monk et al. 2008). Structural studies have also shown differences in amygdala morphology between children with anxiety disorders and healthy controls, although the direction of these findings has been inconsistent (Milham et al. 2005 vs. De Bellis et al. 2002).

The amygdala is part of a larger emotion-regulation network that includes regions of prefrontal cortex that have also demonstrated altered function in pediatric anxiety disorders (see Table 10.1). For example, adolescents with GAD show increased ventrolateral prefrontal cortex (VLPFC) activation in response to angry faces presented for 500 msec (Monk et al. 2006). This result contrasts with a subsequent study that found increased amygdala activation to angry faces presented subliminally (17 msec). This difference suggests that threat is initially processed by the amygdala, and then prefrontal regions such as the VLPFC become involved in regulating that response. Further support for this is provided by functional connectivity analyses showing evidence of reduced negative coupling between amygdala and VLPFC in GAD youth, which is suggestive of reduced capacity to regulate emotion (Monk et al. 2006, 2008).

Recent studies have taken novel approaches to examine these functional alterations in the amygdala and prefrontal cortex using alternative paradigms designed to be more directly relevant for pediatric anxiety disorders (see Table 10.1). First, a recent study by Gayer et al. 2009, published in *Science*, demonstrated that children with anxiety disorders show increased amygdala activation in response to fearful faces presented subliminally (17 msec). This difference suggests that threat is initially processed by the amygdala, and then prefrontal regions such as the VLPFC become involved in regulating that response. Further support for this is provided by functional connectivity analyses showing evidence of reduced negative coupling between amygdala and VLPFC in GAD youth, which is suggestive of reduced capacity to regulate emotion (Monk et al. 2006, 2008).

### Table 10.1 Functional neuroimaging studies among children and adolescents with anxiety

<table>
<thead>
<tr>
<th>Author, Date of publication</th>
<th>Sample</th>
<th>Task</th>
<th>Targeted brain regions</th>
<th>Primary finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lau et al. 2009</td>
<td>Case-control: Adolescent anxiety</td>
<td></td>
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<tr>
<td></td>
<td>Peer evaluation: Peer evaluation</td>
<td>Amygdala, VLPFC</td>
<td>ANX greater amygdala activation than HC. Significant positive amygdala-VLPFC relationship in ANX vs. HC.</td>
<td></td>
</tr>
<tr>
<td>McClell et al. 2007</td>
<td>Case-control: Adolescent anxiety</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Decision-making paradigm: Decision-making paradigm</td>
<td>Amygdala, frontal regions</td>
<td>In ANX, greater intolerance of uncertainty associated with greater activation in amygdala and frontal regions.</td>
<td></td>
</tr>
<tr>
<td>Monk et al. 2006</td>
<td>Case-control: Adolescent anxiety</td>
<td></td>
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<tr>
<td></td>
<td>Attention-orienting paradigm: Attention-orienting paradigm</td>
<td>Amygdala, VLPFC, ACC</td>
<td>ANX show greater activation amygdala, VLPFC, ACC than HC.</td>
<td></td>
</tr>
<tr>
<td>Monk et al. 2008</td>
<td>Case-control: Adolescent anxiety</td>
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</tr>
<tr>
<td></td>
<td>Attention-orienting paradigm: Attention-orienting paradigm</td>
<td>Amygdala, VLPFC</td>
<td>ANX greater amygdala activation than HC. Amygdala and VLPFC functionally related during threat task.</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: 5-HTT, serotonin transporter, ACC, anterior cingulate cortex, ANX, anxiety disorder group, HC, healthy control group, VLPFC, ventrolateral prefrontal cortex.
to anxiety disorders has been demonstrated through enhanced reactivity. Second, a recent pediatric fMRI study found a significant association between intolerance of uncertainty and brain responses to uncertainty in adolescents with GAD and/or social phobia (Krain et al. 2008). Cognitive models propose a prominent role of intolerance of uncertainty, which is defined as “the tendency to react negatively on an emotional, cognitive, and behavioral level to uncertain situations and events” (Dugas et al. 2004) in anxiety disorders, particularly GAD. Therefore, understanding the neural basis of this cognitive bias can inform pathophysiological models of how anxiety disorders such as GAD develop. Within the anxious group, those who were more intolerant of uncertainty showed greater activation in frontal and limbic brain regions than did youth with low uncertainty tolerance. Although this study did not find a difference between anxiety-disordered and control youth, it represents an important step in understanding the relationship of specific traits or features of anxiety, such as intolerance of uncertainty, to underlying neural circuitry. Such findings call into question current nosological boundaries and demonstrate the need for further study of the neural basis of information processing and trait characteristics to inform diagnostic definitions.

Physiological Probes: Panic Disorder

Panic disorder is characterized by panic attacks, paroxysms of acute anxiety often accompanied by changes in respiration (Klein 1993; Pine et al. 2000). This observation has stimulated a series of studies examining respiratory function in adults with this disorder. Much of this work suggests that panic disorder is characterized by enhanced reactivity to innately dangerous situations that elicit changes in respiration. For example, panic attacks can be induced by exposure to substances that change respiratory patterns such as sodium lactate, doxapram, and carbon dioxide (CO₂). Studies in this area generate some of the strongest, most consistent evidence of biological correlates of clinical anxiety. Nevertheless, there remains considerable disagreement, fueled partially by the limited understanding of neural regulation of breathing and hypersensitivity to respiratory provocation, on the ultimate origin behind such enhanced reactivity.

In adults, the relationship of ventilatory physiology to anxiety disorders has been demonstrated through research on enhanced sensitivity to CO₂, manifested as both changes in subjective state and physiology, among panic disorder patients (Klein 1993; Perna et al. 1995). Klein (1993) suggests that these findings reflect an innate sensitivity of the central receptors to signals of possible respiratory compromise. At least among adults, such ventilatory abnormalities have also been identified in first-degree relatives of patients with panic disorder (Coryell 1997; Perna et al. 1995), whereas among children they manifest in patients with possible precursors for panic disorders, such as separation anxiety disorder (Pine et al. 2000) or isolated panic attacks (Perna et al. 1995). Additionally, studies have found family loading for panic disorder in the adult relatives of panic patients with respiratory abnormalities (Perna et al. 1996), suggesting that hypersensitivity to CO₂ inhalation may be a trait marker for panic disorder rather than a state marker. These data suggest that parents with panic disorder may transmit a diathesis for certain forms of anxiety that is observable in the respiratory system (Pine 1999), which may remain latent (Coryell 1997) or may be variably expressed across development as extreme separation distress during childhood or as panic attacks after puberty (Klein 1993; Panksepp 1998; Pine 1999, 2000). Nevertheless, the limited available work among childhood offspring of parents with panic disorder does not support these possibilities. Namely, healthy pediatric offspring of parents with panic disorder show normal responses to CO₂ inhalation (Pine et al. 2005).

These physiological investigations, along with evidence of strong familial associations, provide evidence that childhood SAD and adult panic disorder share a biological substrate (Pine 1999). Similarly, both SAD and children and panic disorder in adults are associated with abnormalities within the noradrenergic system that may contribute to risk for these conditions (Sallee et al. 2000). One major question concerns inconsistencies in the data for physiological measures. For example, innate hypersensitivity in chemoreceptors should be reflected in physiological responses to stimuli such as CO₂, but the data are more consistent for subjective than for ventilatory indices of CO₂ hypersensitivity. Ventilatory measures may be used to refine understandings of endophenotypes, categories that refer to more homogenous groups of individuals with a disorder or a latent risk for a disorder. Despite these limitations, research in this area has significantly advanced conceptualizations of biological markers in anxiety disorders.

Genetic Factors and Psychopharmacology

Given that early life processes can have long-term implications related to the pathophysiology of anxiety disorders, understanding genetic risk factors has become increasingly important. Lau and Pine (2008) explore a mechanism through which genes are expressed in a review of gene–environment interactions on pediatric anxiety. Specifically, genes confer an increased vulnerability to environmental stressors that can contribute to
1 changes in neural circuitry. Individuals with greater
2 genetic vulnerability can establish atypical neural
3 responses when faced with stressors. Over time, atypi-
4 cal connections can contribute to psychological deficits
5 in threat identification and appraisal, which can result
6 in clinical symptoms of anxiety. Although several crite-
7 ria have been explored to determine endophenotypes,
8 the genes involved in pediatric anxiety disorders remain
9 largely unknown. Still, the identification of genetic
10 markers holds the promise of informing predictive
11 models and disorder-specific nosology, as well as treat-
12 ment protocols for pediatric anxiety disorders.

One candidate genetic marker extensively studied
13 by Hariri and Weinberger (2003) is a functional poly-
14 morphism in the promoter region of the serotonin
15 transporter gene (5-HTTLPR). Genetic variation in
16 5-HTTLPR, namely having at least one copy of the
17 short allele, has been found to impact many aspects of
18 functioning including anxiety traits. Neuroimaging
19 studies have found that healthy adult and pediatric sub-
20 jects with at least one short allele have increased
21 amygdala responses to fearful stimuli as compared to
22 those with the typical alleles, similar to anxious youth.
23 In one study, this difference accounted for roughly 20%
24 of the total variance in the amygdala response to fear
25 stimuli (Hariri et al. 2003). These findings provide
26 evidence for a genetic basis of the brain’s response to
27 environmental stressors. Interestingly, some evidence
28 suggests that different associations between 5-HTTLPR
29 and amygdala function manifest in healthy and anxious
30 children and adolescents (Lau et al. 2009). Future stud-
31 ies are needed to determine the developmental impact
32 of 5-HTTLPR alleles by utilizing longitudinal models
33 and exploring gene–environment relationships in pedi-
34 atric populations, including both healthy and anxious
35 individuals.

In light of these genetic findings, attention has focused
36 on the role of serotonin in anxiety disorders. Although
37 studies in adults reveal some evidence of serotonergic
38 abnormalities, virtually no research in this area has
39 been extended to pediatric populations (Charney &
40 Bremner 2001; Pine 1999). Emerging data from therapeu-
41 tic studies, however, do strongly implicate the sero-
42 tonergic system in both adult and pediatric anxiety
43 disorders. The selective serotonin reuptake inhibitors
44 (SSRIs) effectively treat virtually all forms of adult anx-
45 iety. Studies of pediatric anxiety disorders have demon-
46strated positive effects of fluvoxamine for children and
47 adolescents with social phobia, SAD, or GAD (Research
48 Unit on Pediatric Psychopharmacology Anxiety Study
49 Group 2001). More recently, a large multisite study
50 compared the efficacy of sertraline, cognitive-behavioral
51 therapy, the combination of sertraline and cognitive-
52 behavioral therapy, and a pill placebo in 488 children
53 (aged 7–17) with diagnoses of GAD, social phobia, and
54 SAD (Walkup et al. 2008). Sertraline led to significant
55 improvement in 54.9% of those treated with this medi-
56 cation versus placebo at 23.7%. The combination of
cognitive-behavioral therapy and medication was the
most effective at reducing symptoms (80.7% of those
57 treated). These findings are consistent with those of adult
58 studies and provide evidence of serotonin involvement
59 in the pathophysiology of pediatric anxiety disorders.

Studies have also examined the putative role of nor-
60 epinephrine (NE) systems. The evidence currently indi-
cates a complex dysregulation of NE levels and locus
61 coerulescent firing that may lead to increases or decreases
62 in NE release coupled with altered sensitivities of the
63 pre- and postsynaptic receptors (Ressler & Nemeroff
64 2000). Adults with GAD, panic disorder, obsessive-
65 compulsive disorder, or social phobia exhibit a blunted
66 growth hormone (GH) response to clonidine challenge,
67 interpreted as a subsensitivity of central α₂-adrenergic
68 postsynaptic receptors (Charney & Bremner 2001).
69 Adults with panic disorder or post-traumatic stress
70 disorder, in contrast, exhibit hypersensitivity to chal-
71 lenges with yohimbine, an α₂-adrenergic antagonist.72 Such hypersensitivity is manifest most consistently as
73 increases in subjective anxiety, and it appears specific
74 to these two conditions, as opposed to GAD or major
75 depression. Interestingly, Sallee et al. (1998) reported
76 enhanced GH secretion to clonidine challenge in chil-
77 dren with anxiety disorders, findings that run counter
to data from adults that document blunted GH response.
78 More consistent with data in adult panic disorder, a
79 subsequent study by Sallee et al. (2000) found enhanced
80 anxiety responses to yohimbine, as well as blunted GH
81 response in children with anxiety disorders, particularly
82 among children with SAD.

CONCLUSION

Future Directions

Although recent studies have informed our understan-
92 ding of the pathophysiology of pediatric anxiety disorders,
93 this area of research remains in its infancy. The evolv-
ing development of neuroimaging tools and techniques
95 to investigate neural substrates promises to advance
96 this area of research. Similarly, advances in the basic
97 neuroscience of anxiety and molecular genetics may
98 offer unique opportunities to understand the transmis-
99 sion of these disorders across generations. Of para-
100 mount importance is the need to integrate research
efforts to address issues of developmental vulnerability
101 and to explore factors associated with resilience. For
102 example, considerable work in rodents implicates
103 the prefrontal cortex in regulation of fear responses.
104 Perhaps the most extensive work in this area demon-
105strates the capacity of medial prefrontal regions to impact
106 amygdala function in the service of fear extinction
107
Development of prefrontal functions in humans may allow children and adolescents to develop similar forms of fear extinction, accounting for the fact that most pediatric anxiety disorders remit. Similarly, persistent anxiety disorders may be those in which this normal developmental capacity fails to mature. As such, failure of prefrontal regions to effectively down-regulate amygdala hyper-responsivity, and interrupt patterns of chronic amygdala activation may account for the development of an anxiety disorder in children at risk. Novel therapies may be those that correct this underlying incapacity (Pine et al. 2009).

Longitudinal studies combining neurobiological, neuroimaging, genetic, and behavioral measures are needed to test these pathophysiological models, with the ultimate goal of advancing early identification, preventive intervention, and effective treatment efforts.

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NEUROBIOLOGY OF EARLY-ONSET ANXIETY DISORDERS