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Temperament and Anxiety Disorders

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As a relatively new contributor to the world of empirical science, the field of psychology has spent the last century working first to prove its scientific underpinnings and then to generate an understanding of human behavior that truthfully portrays the present and accurately predicts the future. This has at times proven quite difficult because the object of study is much less orderly and rule-bound than the target of other disciplines, such as the atom or the cell. However, a consensus has arisen in the last decade that much of this empirical frustration may have been self-inflicted. By subdividing the field into parsimonious and atomic subdisciplines, researchers have created units that are almost by definition ill suited to capturing the complexity and multidimensionality of human behavior. Leaders in the field are attempting to bridge these gaps by forming multidisciplinary research groups that can bring together disparate literatures and methodologies to create a more three-dimensional view of the phenomenon of interest.

This article focuses on the attempt to link early appearing temperamental traits to the later emergence of psychopathology, particularly in the form of anxiety disorders. The discussion defines and characterizes the current understanding of temperament and anxiety as separate constructs; reviews the evidence to date linking temperament and anxiety; and explores the environmental, cognitive, and neural mechanisms that have been suggested as potential mediators for this effect. The article also highlights the strength of bringing together converging data from multiple sources and levels of analysis.

Anxiety and anxiety disorders can have a large affect on the daily functioning of an individual, coloring interactions with both the environment and personal assessments of internal states. The affect can be particularly damaging if anxiety

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first emerges in childhood and adolescence because this has been linked to increases in both the severity and longevity of the disorder [1]. As such, researchers and clinicians have been keen on identifying factors that may predict the emergence of anxiety. In this regard, differentiating the symptoms or characteristics of the disorder may help researchers delineate the multiple pathways to disease [2].

A number of reviews [3–5] have noted a variety of behavioral similarities between shy or inhibited temperament groups and anxious individuals. Both groups are marked by social awkwardness and withdrawal, an avoidant coping style, and a constellation of psychophysiologic markers (Table 1). Because temperament is early appearing, the construct may help outline early risk factors, even before a disorder is visibly manifested.

There are, however, a number of limitations to the potential bridge between temperament and anxiety that should be kept in mind when reviewing the discussion. First, our definition of temperament must be further refined and solidified. As Vasey and Dadds [4] have noted, many of the measures of temperament in infancy and early childhood have been rationally rather than empirically derived. This has led to some confusion within the temperament literature regarding the core characteristics of a particular temperament trait, the observed behavioral phenotype, its developmental concomitants, and its impact on socioemotional development.

Table 1
Defining characteristics shared by anxiety and behavioral inhibition

Behavior	Characteristics
Overly sensitive danger detection systems	Anxious and behaviorally inhibited individuals show a tendency to feel frightened by objects or situations that most individuals experience as nonthreatening.
Attentional bias to threat	Individuals monitor the environment for potential threat. In addition, anxious or inhibited individuals detect and respond to "threat" cues at lower thresholds. This may lead the individual to find the environment more subjectively threatening.
Avoidant coping style	Having detected an environmental threat, anxious and behaviorally inhibited individuals often respond by withdrawing from the situation and avoiding the trigger both at that moment in time and in future encounters.
Psychophysiologic patterns	Electroencephalographic asymmetry: likely to show greater activation in the right frontal lobe Startle responses: greater potentiated startle to threat cues Heart rate and heart rate variability: show high heart rate and low heart rate variability at rest Pupil dilation: show greater dilation during cognitive tasks Salivary cortisol: tend to show higher levels of stress hormone at rest and after provocation
Over-reactive amygdala	The preliminary definition of behavioral inhibition was based on behaviors linked to amygdalar activity. Recent functional MRI studies have documented increased amygdala activation to threatening and salient stimuli for both clinical and temperament groups.

Second, even with a better-defined construct, it is unlikely that research will reveal a clear linear relationship between early emerging traits and later anxiety. Developmental changes often occur as a result of reciprocal interactions between an active child and his or her environmental context, making the child both the producer and product of the environment [6]. As such, attempts to draw a link from early temperament to the later emergence of psychopathology must contend with the fact that a difficult temperament may push a child in the direction of any number of developmental outcomes (multifinality), and the targeted outcome can result from a host of predisposing pathways (equifinality). Research must therefore account for a number of potential moderating factors that can come into play at various points throughout development.

Third, just as temperament must be rigorously defined, our understanding of anxiety and psychopathology in childhood also must be better delineated. Currently, it is unclear whether these disorders can be viewed as equivalent to the adult template, simply shifted down to younger individuals. Alternatively, anxiety may be a truly developmental phenomenon that takes on a unique form and course in the young child. Beyond outlining the link between early temperament and childhood anxiety, we must therefore also examine the relationships between childhood anxiety and anxiety in adulthood.

Anxiety disorders in childhood

Anxiety is marked by a ''sense of uncontrollability focused on possible future threat, danger, or other upcoming, potentially negative events'' [7]. There is a sense of fear and helplessness in anxiety that is coupled with a somatically aroused central nervous system [8]. This leads the danger detection system to be maladaptively engaged [8], making it difficult to regulate emotional responses to potentially threatening stimuli. Unlike the symptoms of severe psychopathology (ie, delusions), anxiety is a normal state of functioning that has been experienced at one point by all children and adults and can often serve an adaptive purpose. Therefore, researchers must delineate the extent and depth of the anxiety state and distinguish between normative and pathologic anxiety.

In doing so, researchers often make the distinction between state anxiety, trait anxiety, and anxiety disorders. State anxiety is defined normally as a measure of the acute or immediate level of anxiety. Trait anxiety, in contrast, is the long-term tendency of an individual to show an anxiety response to environmental events. Across the clinical divide are a cluster of related disorders, which include generalized anxiety disorder, social phobia, simple phobia, panic disorder, post-traumatic stress disorder (PTSD), and obsessive-compulsive disorder. Together, these disorders affect over 20% of the adult population at one point in life and can exact an annual estimated cost of $44 billion in the United States alone [9]. Anxiety also produces a large individual burden, limiting a person's ability to freely navigate his or her environment free of excess worry and fear. Indeed, perhaps the most important distinction between state or trait anxiety and

anxiety disorders is the degree of impairment that occurs as a result of the state (or trait).

Although they are heterogeneous in behavioral profile, the anxiety disorders are believed to share common physiologic or biologic characteristics, in part because they respond to a similar spectrum of drug treatments [10]. For example, the drugs most commonly used work to increase the potency of the main inhibitory neurotransmitter, γ-aminobutyric acid (GABA), or the serotonin (5-hydroxytryptamine$_3$ [5HT]) neurotransmitters. Recent work also has pointed to a shared genetic component. Approximately 30% to 40% of the variance in anxiety can be attributed to genetic variation [11], although the specificity of the genetic predisposition is unclear [12,13]. Overall, the magnitude of the genetic contribution is relatively moderate and is less than for more heritable disorders such as schizophrenia [14], indicating that gene–environment interactions and correlations are most likely particularly important in the emergence of anxiety.

Much of the work to date has focused exclusively on adult populations. Yet, many cases of anxiety (eg, social phobia) first develop during early to mid-adolescence [15], and anxiety is one of the most common psychiatric conditions afflicting adolescents [16,17]. The prevalence of anxiety disorders is between 5% and 10%, and rates of social phobia, particularly, vary from 1.6% to 8.5% [18–21].

Although many childhood anxiety disorders remit within 3 to 4 years [22], they are likely to carry or signal significant risk for further psychopathology, particularly for other anxiety disorders and depression [23,24]. Indeed, adolescent anxiety (or depression) predicts an approximate 2- to 3-fold increase in risk for anxiety in adulthood [1]. Among children there is a high degree of comorbidity between anxiety disorder and depression (approximately 28%), and comorbidity has been linked to more severe anxiety symptoms [15]. There also may be a developmental progression in which anxiety precedes depression, leading to more detrimental outcomes [25].

As such, there is a need for targeted interventions that may help ameliorate early appearing anxiety disorders. This effort would be helped if researchers and clinicians could accurately predict the emergence of anxiety. Recent work has focused on outlining behavioral, environmental, and biologic markers of risk. One of the most promising lines of research has examined early temperamental traits as a predisposing factor for later psychopathology.

Temperament in childhood

Temperament research in both its ancient (eg, Galen) and modern (eg, Thomas and Chess [26]) forms has attempted to account for core behavioral and psychologic traits that appear to shape mood and behavior for an individual across contexts. The idealized definition of temperament points to a stable psychologic profile with a presumed physiologic foundation that creates an enduring pattern of behaviors that are early appearing and consistent across time

and place [27]. Borrowing from Cairns' [28] notion of behavioral epigenesis, Lahey [29] suggests that temperament can be viewed as the simple (basic or nonspecific) form of socioemotional behavior that appears early in development and provides the elemental materials for later, more complex, forms of behavior.

Much of the current work on temperament has focused on early appearing signs of negative affect and its subsequent link to inhibition, shyness, or social withdrawal. This research can be roughly categorized into one of three different approaches: the use of the adult "Big Five" personality traits as a template for childhood temperament; a continuous model of the dynamic relationship between reactivity and self-regulation; and a categorical approach that identifies children based on a discrete cluster of behavioral and psychophysiologic traits. Common to each approach is a focus on "difficult" or "negative" temperament, which is characterized by the presence of negative emotionality coupled with reports that the child's behavior is hard to manage [30].

The first strategy has attempted to map early temperament onto the adult Big Five model of personality. From this view, temperament is the "nonintellectual component or developmental precursor of personality" [4]. In trying to map onto the Big Five, Lonigan and Dyer conducted a large-scale principal component analysis using the Child Behavior Questionnaire [31] (Lonigan and Dyer, manuscript in preparation, 2000), the Emotion, Activity, Sociability, and Impulsivity (EASI) temperament scales [32], and the Positive and Negative Affective Schedule [33]. They found three factors, positive affect (PA), negative affect (NA), and effortful control, which roughly correspond with the adult constructs of surgency and extraversion, emotional stability/neuroticism, and conscientiousness [4]. Similar three-factor constellations have been found in additional independent samples [34,35].

Preliminary work has begun to link individual differences in PA or NA to childhood behavioral difficulties and psychopathology. For example, anxiety and depression show differing relationships with the temperament constructs. That is, although both anxious and depressed children show high levels of negative affect, only depressed children also show low levels of positive affect [36]. Findings such as these may allow researchers to tease apart the multiple mechanisms that can lead to behavioral profiles that appear similar at the surface.

There are a number of issues that remain to be addressed in this model. First, Vasey and Dadds [4] point out that scales that measure putatively the same dimension often have different patterns of association with other temperament dimensions, suggesting a lack of discriminant validity across the questionnaire-based constructs. This is particularly troubling given that little of this work has sought to reinforce the questionnaire data with either direct behavioral observations or psychophysiologic measures. Second, although the model includes effortful control as a third, more executive component of temperament, much of the work has focused on the PA or NA dimensions, hence the notion that temperament is a "nonintellectual" construct. This characterization would seem to limit the applicability of the model as children mature into late childhood and adolescence, the very point at which psychopathology often begins to emerge.

Third, there are little longitudinal data to help reinforce the initial similarities seen in developmental studies. On this point, Roberts and DelVecchio [37] have suggested that the available data on stability [38,39] indicate that temperament becomes more differentiated and hierarchically integrated with age, allowing for more stable temperamental profiles into adolescence and adulthood.

The second strategic approach has looked at the interaction between physical and emotional reactivity and higher order self-regulatory mechanisms in shaping behavior. The relationships between reactivity and self-regulation mechanisms are both genetically inherited and shaped by experience [40]. Reactivity is the individual's responsivity to changes in stimulation, shown at multiple levels of measurement, behavioral, autonomic, and neuroendocrine. Often, this response is seen in individual differences in the latency, rise time, peak intensity, recovery, and time of reaction when the child is confronted with emotionally evocative events. In contrast, self-regulation involves the processes modulating reactivity, including differences in the tendency to approach or avoid evocative people and events, inhibition in the face of stress, and attentional self-regulation. Generally, children are expected to become increasingly regulated over time, as attention and effortful control develop and can modulate initial reactive tendencies.

Although differences in reactivity appear quite early, it is difficult to judge the long-term impact on socioemotional development until the emergence of self-regulatory skills. This will help determine if underlying reactive tendencies are controlled successfully or are manifested in nonadaptive patterns of behavior. Generally, a child's inability to regulate negative affect can be expressed across three realms: behavior (eg, anxious withdrawal), cognition (eg, low self-worth), and psychophysiology (eg, elevated cortisol levels) [41]. The observed outcomes will depend on the strength and persistence of the underlying reactivity relative to the child's ability to draw on personal self-regulatory skills and environmental supports. High levels of negative affectivity have been linked to increased levels of internalizing problems, anxiety, and depression [2], while simultaneously acting as a protective factor against the development of externalizing disorders [42,43].

In measuring these relationships, it is important to note that stability in a temperamental profile across time appears to center on the high-order levels of temperament, rather than on the level of individual behaviors [4]. With development, the triggers for inhibited behavior change, and, similarly, the form of the behavioral response also changes. As such, the dynamic balance between reactivity and regulation must always be approached with the context of the developmental trajectory of the child. However, the assumption is that below the surface changes the underlying trait, at the biologic level, remains stable [41].

The third research approach has focused on behavioral inhibition as one of a number of discrete temperament categories that are evident in nature. Behavioral inhibition is found in approximately 15% of the population and is defined as the tendency to display signs of fear and wariness in response to unfamiliar stimuli [44–46]. As infants, behaviorally inhibited children show high levels of negative reactivity. That is, they respond with negative affect and vigorous activity when

confronted with novelty. Later in life, behaviorally inhibited children are often "slow to warm up" in new social situations [47] and display unregulated social behavior that is characterized by social withdrawal to unfamiliar peers [48]. They are unlikely to initiate interaction, and they often do not respond positively when social initiations are made toward them [49].

Unlike the previous models, behavioral inhibition is defined by a constellation of traits at both the behavioral and psychophysiologic level. Specifically, inhibited children show a high- and low-heart rate variability [50,51], pupillary dilation during cognitive tasks [45], elevated salivary cortisol levels [46,52], an increased startle response [45,47,53], and right frontal electroencephalographic (EEG) asymmetry [50,54–57]. This profile is believed to be at least partially genetically mediated. For example, a recent study [58] found a strong link between behavioral inhibition and an allele of the corticotropin-releasing hormone, which is a key mediator of the stress response as it acts on the hypothalamic-pituitary-adrenal axis and the limbic system.

Long-term studies have noted moderate stability of behavioral inhibition from toddlerhood through middle childhood [59], from preschool age to middle and late childhood [60], and into early adulthood [39]. Among children selected for behavioral inhibition, Pearson correlations between repeated testing sessions, beginning in toddlerhood and ranging over 1 to 6 years, have been between $r = 0.24$ and $r = 0.64$ [60–63]. The correlations are higher among the extremely inhibited children [47]. In unselected samples, inhibition is shown to be moderately stable ($r = 0.33$–0.42) among preschoolers over the course of 2 years [64]. Again, extreme groups show much higher levels of stability, even over the course of 4 years [65].

In defining behavioral inhibition, Kagan [66] proposed that the observed physiologic and behavioral traits were linked to variations in amygdalar responses. In doing so, he drew on a line of research linking the amygdala to the acquisition of conditioned fear [67], the induction of vigorous limb movements [68], and the modulation of distress cries [69]. Behaviorally inhibited children appear to have an over-reactive amygdala, triggering a highly responsive sympathetic nervous system when confronted with stressful stimuli [46,70,71]. The role of the amygdala in behavioral inhibition and anxiety will be discussed in greater detail below.

Link between early temperament and childhood anxiety

Although research has generated a strong set of findings that help to characterize the form and function of temperamental traits, work linking early temperament to later risk for psychopathology is relatively new, limiting the conclusions that can be drawn concerning this relationship [72]. Frick [73] points out that the primary focus of research on temperament has been on its manifestations in infancy and early childhood. In contrast, research on psychopathology has understandably focused on its emergence in late childhood and

adolescence [74]. As such, progress in the field will need to bridge developmental and clinical psychology, merging different theoretical constructs, research goals, research populations, and experimental methods [73,75].

Some investigators [4] argue that the low base rate of psychopathology makes studying the link between temperament and disorder difficult. However, a growing number of studies have found a persistent link between temperament-based negative affect in early childhood (variously defined) and the emergence of anxiety in mid to late adolescence [76–78]. Indeed, emerging data [77,79] suggest that the rate of psychopathology may be quite high at the temperamental extremes.

This section reviews the current descriptive findings concerning this relationship. The discussion will then turn to the mechanisms that may account for the findings to date.

The presence of behavioral inhibition in early childhood has been shown to be a risk factor for anxiety in childhood [80,81] and adolescence [77,82], particularly with regard to social phobia [77,83]. The link is strongest among adolescents who display consistent signs of inhibition across multiple testing points in childhood [84,85].

For example, a recent report [86] has found that 15% of young adults identified previously as behaviorally inhibited toddlers were diagnosed with generalized social phobia. Schwartz and colleagues [77] have found that adolescents who were inhibited at the age of 2 are more likely than their uninhibited peers to show symptoms of social anxiety as assessed by a semistructured diagnostic interview (ie, diagnostic interview schedule for children [DISC]). Indeed, 61% of the adolescents had current symptoms, and 80% had shown symptoms of anxiety at one point in their lifetime.

Using a Big Five perspective, Lonigan and colleagues [87] have found similarly that across 7 months fourth and 11th graders who were high in negative affect were likely to show increased levels of anxiety. Coupled with low levels of positive affect, negative affect also was predictive of increases in depression. Masi and colleagues [88] have found that the diagnosis of anxiety or anxiety comorbid with depression in adolescence is significantly linked to parental reports of emotionality and shyness, using Buss and Plomin's [89] EASI scale. The other two factors, activity and sociability, did not distinguish between the diagnostic groups and the controls. With regard to the emotionality and shyness scales, Buss and Plomin [89] suggest that these two factors in combination can be considered grossly equivalent to Kagan and colleagues' [70] construct of behavioral inhibition. Although direct comparisons of the two measures will be needed to confirm this relationship, it does suggest a stable core trait imparting risk in these children.

A study by Kagan and colleagues [90] has argued that because the relationships between temperament and socioemotional outcomes are nonlinear, it is important to examine subjects who have extreme scores. This will allow a clear differentiation across temperament groups because, in Kagan's formulation, individuals with extreme scores constitute discrete populations who have unique

properties and developmental trajectories. In line with this admonition, Hayward and colleagues [91] have found that adolescents rated in the top 15% of self-reported behavioral inhibition had a 5-fold increase in developing social anxiety, relative to peers without an extreme temperamental profile.

Also in line with the notion that the relationship is clearer in extreme or discreet populations, a number of studies have found a clear link between temperament and anxiety in children of parents with panic disorder. Biederman and colleagues [83] have found that the rate of social anxiety disorder was significantly higher in inhibited children relative to children without behavioral inhibition. Although the interaction with parental diagnosis was not significant, the main effect of the behavioral inhibition group held only for those children who had a diagnosed parent. In addition, parallel studies have found that children of parents with anxiety disorders are more likely to show extreme behavioral inhibition [92]. A summary of these and other findings can be found in tabular form in Hirshfeld-Becker and colleagues' [93] review of the studies linking behavioral inhibition to vulnerability to psychopathology.

These initial results were not surprising given that researchers have long noted the surface similarities between negative affect and anxiety in both their operational definition and observed behavioral patterns (see Table 1). First, for example, Rapee [94] has suggested that a major component of withdrawn temperament is an avoidant style of coping. In turn, an avoidant coping style also is a central characteristic of children with clinical anxiety disorders [95].

Avoidance may help distinguish the shy child from other temperament or personality groups. For example, when they are given ambiguous social scenarios [96], withdrawn and oppositional children are highly likely to indicate a perceived threat. However, when asked to characterize their response to the threat, only the withdrawn children outlined an avoidant style. There are additional data indicating that mothers of withdrawn children may actively promote avoidance in their children [97].

Second, both anxiety and behavioral inhibition have been linked to difficulties in the deployment of the danger-detection system [8]. The tendency to feel frightened by objects or situations that most individuals experience as nonthreatening represents a cardinal feature of most clinical anxiety disorders. This increased tendency to experience the subjective state of fear is associated with a variety of cognitive correlates, including thinking about feared objects or situations when they are not present, scanning the environment for signs of danger, and neglecting other nonfrightening aspects of the environment.

In particular, two studies using positive and negative facial expressions have found an explicit memory bias for negative or critical faces in social phobics [97,98]. Social phobics also have been found to display an attentional bias to words conveying a social threat [99,100]. Similarly, negative reactivity to novelty early in the first year of life is linked to a negative bias in information processing and social cognition.

Questions remain concerning the functional and structural relationships between temperament and anxiety. Temperament can either place a child at risk

for developing certain forms of psychopathology or influence the stability or severity of the disorder [101]. This conceptualizes temperament as a separate construct from psychopathology [73]. Alternately, psychopathology could be construed as the extreme endpoint along a single temperamental spectrum [101]. The cut off between individual variation and psychologic disorder would be drawn when the child experiences psychosocial impairments [73]. Indeed, Lahey [29] argues that there is no inherent distinction between temperament and psychopathology in nature. Distinctions are simply imposed by experts in the field, taking into account the data revealing interconnections between basic temperamental traits (eg, irritability and anger) and specific psychopathologies (eg, oppositional defiant disorder). Along these lines, Akiskal [102] sees temperament as a subclinical variant of psychiatric disorders. This would be particularly the case among the extreme temperament types or spectrum.

Potential explanatory mechanisms

To date, the explanatory research has focused on three broad areas: environmental and parenting factors, cognitive or attentional mechanisms, and variations in neural functioning (particularly the amygdala and the orbital frontal cortex [OFC]).

Animal model for parenting

The literature in both the animal and human models suggests that parents and parenting style can influence the presence of negative temperament and the eventual emergence of anxiety. In doing so, the link appears to rely on both heritable traits passed along across generations and the parenting styles that color day-to-day interactions.

For example, in rat models, maternal licking of pups is believed to reflect the ''conscientiousness'' of the mother and is used as a marker for maternal effectiveness. Pups raised by mothers with impaired licking and grooming skills have higher levels of anxiety-related behavior than pups raised by high licking-and-grooming mothers [103]. Cross-fostering to a high-licking mother after birth will decrease anxiety-related behavior developing in the offspring of low-licking mothers [104]. However, the offspring of high-licking mothers will not take on the high-anxiety behaviors of their low-licking foster-mother. Francis and colleagues [105] have also shown that experimentally conferred high licking-and-grooming behavior can be passed on across generations. Females raised by high-licking mothers go on to become high-licking mothers themselves and have low-anxiety offspring, regardless of their genetic lineage.

These data suggest that although anxiety-related behaviors are amenable to environmental change, the buffering factors that protect an individual from disorder may be difficult to overcome, crumbling only in the face of multiple

or severe insults. To examine the extent of the gene–environment dynamic, Francis and colleagues [105] transplanted embryos from a high-licking strain of mothers into a low-licking strain of surrogate mothers shortly after conception. The authors found that to confer low-licking behavior on the offspring of high-licking rats, the offspring must have exposure to a low-licking mother both in utero and after birth. No other combination of gestational and infant care produced low-licking rats. These data suggest that maternal characteristics that appear to shape behavioral outcomes begin to act long before birth. Although gestation may set the stage for later risk, this vulnerability must be reinforced early in life to have long-term consequences. Many of these issues are being explored in the human literature. Here, two factors have emerged as particularly important: parental intrusiveness or insensitivity and a parental history of anxiety disorders.

Parenting style

Thomas and Chess [26] were the first to introduce the concept of ''goodness-of-fit'' in arguing that the link between temperament and later adjustment cannot be understood without accounting for the dynamic characteristics of the child's environment, both in isolation and in direct response to the child's temperamental traits. Since then, a long line of research has argued that parenting styles, such as overprotective and controlling behavior and criticism and lack of warmth, are linked to the emergence of anxiety in children [106,107]. Sensitive parenting encourages mutual regulation between parent and child and contributes to the child mastering his or her own behavior [108]. In contrast, intrusive parenting may disrupt mutual regulation and interfere with the development of self-regulation [109]. A lack of strong self-regulatory skills would leave the child more vulnerable to underlying reactive tendencies.

Rubin and colleagues [110] have investigated whether the interaction of parenting behaviors and behavioral inhibition at 2 years of age explained child characteristics at 4 years of age, either directly or through the moderation of earlier inhibition. A maternal parenting style consisting of overly warm, intrusive, unresponsive, and derisive behavior moderated the concurrent association between shyness and behavioral inhibition at 2 years [111]. These associations remained 2 years later when children were reassessed at 4 years of age [110]. Inhibition at 2 years only predicted reticence with unfamiliar peers at 4 years when mothers behaved in a psychologically controlling or derisive manner.

Also affecting this relationship is the use of nonparental care. Fox and colleagues [56] have found that infants who show high negative emotionality at 4 months of age are more likely to change their behavior and become less inhibited over toddlerhood when they are placed in nonparental caregiving environments for at least 10 hours per week. Children who stay at home may be more likely to receive parenting that is more overcontrolling and oversolicitous, whereas children who go to daycare may be more likely to receive parenting that fosters independence [112]. In addition, children in out-of-home care have much

more experience interacting with unfamiliar adults and peers, further ameliorating underlying reactive traits. Future work will need to determine if parenting style and care environment are risk factors independent of temperament or are directly associated with temperament [94].

Parental psychopathology

Parental behaviors, particularly when colored by the presence of mood or anxiety disorders, may mitigate or exacerbate the onset or maintenance of behavioral inhibition [113,114]. Several previous studies have reported higher risks of behavioral inhibition in children of adults with anxiety disorders [80,115] or major depression [116,117] as well as increased rates of parental anxiety disorders in children with inhibited behavior.

In examining this link, a number of potential moderating factors have been tested. Hirshfeld-Becker and colleagues [118] have found no relationships among behavioral inhibition and any of the following measures of psychosocial adversity: family conflict, low socioeconomic status, large family size, exposure to psychopathology, and paternal criminality. These data suggest that psychosocial factors cannot account for the link between behavioral inhibition and maternal psychopathology. Rather, the data bolster the contention that behavioral inhibition is quite heritable, with estimates ranging from 0.40 to 0.70 in twin studies [119–121].

Masi and colleagues [88] have found that the siblings of anxious adolescents, although free of psychopathology, also showed significantly higher levels of emotionality and shyness compared with the siblings of the children in two control groups. This suggests a shared genetic diathesis that can predispose a child to psychopathology. Indeed, high levels of emotionality were found in both the mothers and fathers of the anxious-depressed children. However, without a precipitating event or insult, this predisposition may not cross the line into a psychiatric diagnosis.

Overall, the data suggest that children who have inherited an inhibited temperament and are more sensitive to adversity factors may find it particularly daunting when challenged by a poor parenting environment colored by psychopathology. Yet, although the presence of a parent with panic disorder will predispose a child for panic disorder and other anxiety disorders [115–122], not all children will become ill. As such, additional features either internal or external to the child must be brought into the equation to more effectively assess risk and apply needed interventions [83].

Escalona [123] points out that simply noting the presence of an environmental stressor is not sufficient for understanding the impact on the child or child's response to the stressor. Rather, researchers and theorists must work to capture the child's "effective experience." As such, a second line of research has looked at child-centered variables to understand the relationships between early temperament and anxiety. The most heavily examined phenomenon involves individual differences in attentional or effortful control.

Attentional or effortful control

Flexible cognition and attention requires the ability to carry out two opposing processes: selecting goal-related stimuli for processing and detecting potentially significant and often unpredictable events [124]. Individuals must simultaneously and selectively deploy attention and filter out distracters outside of this realm, although at the same time they must allow for changes in the outer realm to intrude on the focus of attention when potentially significant. This delicate balance allows individuals to proceed through their daily activities without undue burden or disturbance. When the balance is lost, a cascading effect of successive cognitive and affective processes can lead to patterns of behavior that are maladaptive or disordered.

A number of researchers have suggested that among children with temperamental behavioral inhibition, children who are able to harness attentional control mechanisms can mitigate underlying reactive tendencies and avoid deleterious effects. In contrast, behaviorally inhibited children with poor control skills would be more beholden to initial affective reactions to external stimuli and would be more likely to show symptoms of anxiety. Thus, the coping resources available to the child may moderate the physiologic and behavioral correlates of temperament [125].

When these coping mechanisms are ineffective, negative characteristics often linked to anxiety are then observed. For example, when presented with ambiguous situations, young socially anxious children perceive threat more quickly and report more negative feelings [126]. Anxious children also have more negative cognitions and make lower estimates of their competency to cope with dangerous or stressful events [127]. In these cases, the child has proven unable to filter out the ambiguity and threat of the situation and focus on more positive and adaptive behaviors.

Temperamentally reactive children often react to threat or stress in two somewhat paradoxical ways. First, they show an avoidant coping style [94] and often retreat from direct engagement. Second, they will continue to monitor the potential threat, showing an attentional bias for such environmental stimuli. This could lead the anxious individual to find the environment more subjectively threatening.

Both trait anxious [128–130] and clinically anxious [131–133] adults appear to display an attentional bias toward threatening information. The data suggest that high- and low-trait anxious individuals show a similar quadratic function toward threat. That is, all individuals shift attention away from mild threat and toward intense threat. However, with stimuli of moderate intensity, the high-trait anxious individual will show a larger attentional bias toward the stimuli, relative to the low-trait anxious counterpart. This can be conceived of as a shift in phase for the function [134–136].

Although the data are preliminary, early findings indicate that anxiety-related attentional biases operate similarly in children and adults [137]. Parallel findings have been noted with clinically anxious [138,139], high-trait anxious [140]

(Vasey and Schippell, manuscript in preparation, 2002), and behaviorally inhibited children [141]. For example, Vasey has found that in children with low effortful or attentional control, high levels of anxiety predicted a bias in favor of threat cues (M.W. Vasey, unpublished data, 2003). Interestingly, the relationship did not hold for children with good attentional control skills, suggesting that regulatory mechanisms can act as a buffer in the face of negative reactivity tempering the normal socioemotional consequences.

Rothbart and colleagues [142] have shown that individuals who are better equipped to regulate initial reactivity, particularly through the use of attentional mechanisms, are less likely to show prolonged periods of negative affect. For example, their data suggest that infants prone to distress are less adept at shifting attention away from a distressing stimulus and have difficulty engaging in self-soothing activity [142,143]. In addition, data from the present authors' temperament cohort showed that mothers of 9-month old infants who show poor attentional control rate the infants as prone to distress and less likely to show spontaneous smiles (Pérez-Edgar, Martin, and Fox, manuscript in preparation, 2005). At age 4, these children also showed greater signs of social reticence.

As such, Mathews and MacLeod [144] suggest that the ability to effectively override initial reactive tendencies or biases is what distinguishes the healthy high-trait anxious individual from his or her counterpart who exhibits clinically relevant levels of anxiety. Lonigan and colleagues [5] have suggested that documenting the following six findings would help to empirically support the notion that effortful control moderates the relationship between affective reactivity and anxiety: (1) Negative affect, positive affect, and effortful control are shown to be distinct factors with significant stability over time; (2) there are unique relationships between negative affect and effortful control with anxiety; (3) the strength of the relationship between negative affect and anxiety is at least partially dependant on the individual's level of effortful control; (4) the strength of the effect of effortful control will vary with performance conditions, particularly with respect to the timing of processing and response production; (5) effortful control does not moderate the relationship between negative affect and pre-attentional threat bias; and (6) a significant portion of the relationships between negative affect and effortful control with anxiety can be accounted for by attentional bias. Once systematic research programs are able to address each of these points, we should have a fuller picture of the role attention and attention regulation plays in the development and maintenance of anxiety.

Neural underpinnings

Paralleling the work examining reactivity and regulation in cognition and behavior, neuroscientists have begun to examine the balance between reactive neural structures (ie, the amygdala) and more regulatory structures (ie, the OFC). Although 20 years of work pointed to the role the amygdala may play in inhibited temperament [47,56], direct examination of this brain structure has only recently

become available with the widespread adoption of MRI and functional MRI (fMRI) technology for research [145].

Previous work has linked the amygdala to the fear system. Fear induction through the injection of procaine [146] or cholecystokinin tetrapeptide (CCK4) [147] will produce amygdala activation in healthy adults. In addition, studies have demonstrated greater amygdalar activity to fearful versus happy [148] or neutral [149,150] facial expressions. Amygdalar activity also has been seen in response to threatening words [151], signals predicting shock [152], and aversive odors and tastes [153].

Individuals who have amygdalar damage but intact hippocampi do not acquire conditioned skin conductance responses (SCR) despite verbalizing the stimulus association [154]. In contrast, individuals who have an intact amygdala and damaged hippocampi cannot state the conditioned association while showing the expected SCR to the presentation of the conditioned stimulus [155]. The amygdala also activates when the contingencies between a stimulus and a negative outcome are unpredictable [156] or when the level of threat is ambiguous, requiring increased vigilance [157].

Recent work has suggested that the amygdala, beyond being integral to the fear system, also is involved in salience detection without regard to the hedonic value of the environmental stimulus. To that end, Baxter and colleagues [158] have noted that individuals with amygdalar damage are deficient in their ability to use information about positive and negative outcomes to guide their choice behavior. Indeed, the role of the amygdala in stimulus–reward learning might be just as important as its role in processing negative affect and fear conditioning [159], as can be seen in a series of studies examining reinforcement and learning in traditional Pavlovian paradigms [160,161].

Imaging studies of subjects who differ in temperament are still few in number. However, the first major study [162] has found that young adults (mean 22 years of age) categorized as inhibited in the second year of life showed significant bilateral amygdalar activation to the presentation of novel faces, versus fixation, relative to participants without a history of behavioral inhibition. Although imaging studies of anxious children are emerging only now, the recent work has been promising. For example, Monk and colleagues [163] have found that children fearful of an uncomfortable air puff to the larynx will show more right-sided amygdalar activation when faced with the threat of the upcoming air puff. In addition, children with anxiety disorders display hyper-responsive amygdalar activity compared with healthy children of the same age when viewing fearful versus neutral faces, particularly in the right hemisphere [164].

Potentially tempering reactivity within the amygdala is the orbital frontal cortex. The OFC is situated in the anterior and medial regions of the prefrontal cortex and is the only region in the prefrontal cortex that has strong reciprocal connections with the amygdala (Fig. 1) [165,166]. These connections may help explain the data suggesting that the amygdala also is closely involved in more complex social judgments, beyond the simple recognition of fear. For example, the amygdala appears to play a role in judging trustworthiness and approach-

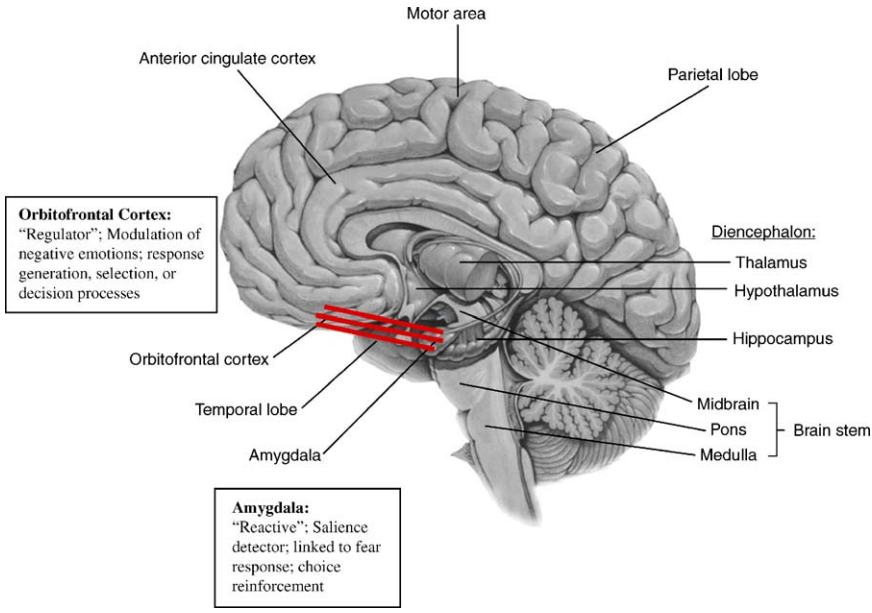

Fig. 1. Reciprocal connections between the amygdala and the orbitofrontal cortex (*black bars*). These connections may serve as the neural underpinnings for the relationships between reactivity and self-regulation noted in behavioral studies of temperament and anxiety.

ability, traits that require processing multiple complex cues [167]. In this regard, the OFC is linked to the modulation of negative emotions [168] and is critical for response generation, selection, or decision processes [161], as well as an adaptive change of behavior in the face of environmental consequences [169]. As such, according to Davidson and Irwin [170], damage to orbitofrontal areas "would not impair immediate reactivity to incentives, but. . .the capacity to sustain and anticipate such reactions when the immediate elicitors are not present." Similarly, the use of reinforcers to guide response selection also requires the interaction of the amygdala and OFC [158].

Animal and adult studies have correlated OFC damage with increased anxiety, affective lability, social disinhibition, and increased aggression [171–173]. Individuals with OFC lesions also appear to act more impulsively in both cognitive–behavioral tasks and in self-reported measures [174]. This impulsivity could be related to a tendency to respond rapidly to rewards and punishers without assessing the consequences sufficiently. It also points to a failure to self-regulate on the part of OFC patients. That is, although these individuals are fully aware of their impulsivity (or disinhibition and socially inappropriate behavior), they are unable to prevent themselves from acting out in such a manner.

Within the realm of anxiety disorders, multiple studies of adults with simple phobias document dysregulation of the orbitofrontal cortex during the presentation of symptom-arousing stimuli [175,176]. In social phobias, adults show

increased amygdalar activity to neutral faces [177]. Increased amygdalar activation and decreased orbitofrontal cortex activity during a fear-provoking task [178] have also been documented.

Outstanding issues

Kagan and colleagues [90] have suggested that research is a ''contest in which [nature] presents a sign and investigators try to determine its meaning, especially those features. . .that reveal the origin of the natural event.'' As noted here, the literature is beginning to suggest that a specific temperament accounts for a large amount of the variance in the development of anxiety disorders. Temperament may set the stage by shaping the child's early reactive and affective biases. It may then influence the child's ability to modify these inborn tendencies through individual differences in attentional and effortful regulation. These differences can be seen at the behavioral and psychophysiologic level, and preliminary work suggests that there are stable neural underpinnings for the observed differences.

If these observations prove correct, there are large implications for how researchers and clinicians should address the issue of childhood anxiety. However, there are a number of issues that first must be addressed before our understanding of the temperament-anxiety link may be usefully translated into effective, targeted interventions.

First, our constructs of temperament and anxiety must be carefully and fully defined. The lack of progress in this area may in part reflect the predominance of univariate and unidimensional approaches. In 2001, Kagan and colleagues [27] warned against assuming that anxiety and temperament are unitary natural phenomena that require only a simple consensus definition. In particular, the authors are concerned that the terms are traded back and forth within the literature without a solid grounding in the context in which they are experienced or observed. To study the phenomena most parsimoniously and parse out the root causes, the various forms of anxiety and temperament must be delineated. For example, the researcher must be careful to distinguish between the acute state of anxiety (eg, after a negative life event) and the chronic state of anxiety (eg, as part of a general personality trait), each of which may differ in their relationship to temperament and the added risk for the emergence of disorder.

From this point of view, the strongest data can be found in constructs that draw from multiple streams, including behavioral observation across contexts, parent- and child-reporting, and psychophysiology. This will allow researchers and clinicians to see fully the intersections between temperament and anxiety, better delineating which children are at greatest risk for future disorders and which shared traits, if any, are amenable to intervention.

Second, research must expand to encompass a broader time frame, examining the developmental trajectories of temperament and anxiety from infancy through middle childhood and adolescence and into adulthood. Because many of the studies to date that have examined the link between temperament and psy-

chopathology has focused on fairly young children, it is possible that an additional or differing pattern of diagnoses will emerge over time with development and maturation. For example, it appears that the negative consequences of shyness or inhibition reach a peak in the adolescent years, in terms of difficult social encounters [179], poor self evaluations [180], and the emergence of compromising psychiatric problems [181]. To push the timeline even farther, the relationship between childhood or infant temperament and adult personality remains exceedingly unclear.

This suggests that the careful study of developmental trends in adolescence may prove an informative conduit, reinforcing the power of detailed longitudinal studies. Extended longitudinal studies will help confirm the long-term stability of psychopathology seen in adolescence. Presently, we do not know truly if the current findings are transient in nature, responding to the unique stressors of adolescence, or harbingers of life-long difficulty and disturbance.

Ollendick and Hirshfeld-Becker [182] suggest the following types of studies would be helpful in testing the viability of developmental psychopathology models of anxiety: (1) longitudinal prospective studies that identify temperamentally vulnerable children early in life and also monitor parental behavior and peer influences; (2) twin studies that assess both behavioral inhibition and childhood anxiety disorders; (3) adoption studies of at-risk children that assess both environmental and genetic risk factors; and (4) interventional studies of at-risk offspring who have behavioral inhibition.

This work also will help determine if the cognitive and neural measures noted above are markers for psychiatric vulnerability or are the actual symptoms of a disorder. Observed biologic differences across control and diagnostic groups should not be assumed to reflect a specific marker for the disorder; rather, the difference may point to a risk factor, or diathesis, that preceded the onset of the disorder and is shared with at-risk but healthy counterparts of the diagnostic group [145]. For example, several researchers have found decreased hippocampal volumes in individuals with PTSD [183], leading many investigators to propose that the decrease is a direct consequence of the individual's chronic state of stress [184,185]. However, recent studies examining twins discordant for PTSD have found that both twins show reduced hippocampal volumes, indicating that decreased size is a risk factor for PTSD, not a sign of the disorder [186].

If the link between temperament and anxiety does hold, targeted interventions must then tackle the question of how amenable core temperament traits may be to modification. There is some evidence that active attempts by parents to alter their child's worrisome temperament can nudge a child toward the mean in social behavior [70]. Preliminary data also indicate that early peer exposure through daily out-of-home care also can ameliorate early signs of inhibition [56]. In each case, systematic work is needed to test these relationships. Along these lines, Rapee [94] is currently testing an intervention protocol designed to decrease the likelihood of developing anxiety in inhibited children ages 3.5 to 4.5 years old. Preliminary data indicate that the intervention markedly decreases signs of inhibition and anxiety at a 1-year follow-up.

Summary

The broad range of issues touched on in this article highlights our view of temperament and psychopathology as complex, multidimensional phenomena that are embedded within multiple causative pathways and which, in turn, produce any number of developmental outcomes. As such, it seems clear that any future progress is almost wholly dependent on our ability to forge multidisciplinary research programs that can address the link between temperament and anxiety from multiple levels of analysis across both time and contexts. This will allow the field to come closer to the larger goals shared across psychology: description, prediction, and intervention.

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