

# Research Review: A neuroscience framework for pediatric anxiety disorders

**Daniel S. Pine**

Section on Development and Affective Neuroscience, National Institute of Mental Health Intramural Research Program, Bethesda, MD, USA

Across a range of mammalian species, early developmental variations in fear-related behaviors constrain patterns of anxious behavior throughout life. Individual differences in anxiety among rodents and non-human primates have been shown to reflect early-life influences of genes and the environment on brain circuitry. However, in humans, the manner in which genes and the environment developmentally shape individual differences in anxiety and associated brain circuitry remains poorly specified. The current review presents a conceptual framework that facilitates clinical research examining developmental influences on brain circuitry and anxiety. Research using threat-exposure paradigms might most directly integrate basic and clinical perspectives on pediatric anxiety. **Keywords:** Anxiety, children and adolescents, amygdala, prefrontal cortex, threat.

Recent research on mental illness establishes two organizing principles: most chronic disorders have roots in childhood; disorders reflect individual differences in brain function. While these observations suggest that mental disorders emerge from individual differences in neurodevelopment, limited work links disruptions in brain function to specific developmental pathways associated with particular clinical states. This review illustrates the manner in which studies of information processing in pediatric anxiety facilitate attempts to integrate developmental psychopathology and neuroscience. Work in other psychopathologies, focusing on different information processing functions, may allow similar integration. Work on anxiety focuses on information processing functions with adaptive value that become engaged based on situational threats and an organism's goals. Anxiety disorders involve biases in these processes, such that elicitation of threat-related processes emerges in inappropriate contexts.

DSM-IV recognizes more than 10 anxiety disorders characterized by extreme distress or avoidance about threats or danger. Due to cross-disorder similarities, it remains unclear if anxiety disorders represent discrete entities or manifestations of one underlying process, leading some to suggest that distinctions among the anxiety disorders are trivial (Buckley, Michels et al., 2006). This article reviews evidence of both disorder-specific and shared pathophysiology. Where disorder-specific pathophysiology is considered, the review focuses on social phobia (SOPH), separation anxiety disorder (SAD), and generalized anxiety disorder (GAD).

This review unfolds in three stages. The initial section summarizes recent findings in developmental psychopathology and affective neuroscience. The middle section provides an integrative perspective on

pathophysiology that uses data on information processing to relate clinical and basic approaches. The final section illustrates the way in which this perspective facilitates an integration of basic and clinical work through brain imaging.

## Developmental psychopathology and affective neuroscience

Events during development lay the groundwork for long-term patterns of threat response behavior and physiology. The consistencies in data across laboratories, research paradigms, and even across mammalian species speak to the applicability of integrative perspectives.

### *Developmental psychopathology*

*Pediatric anxiety.* Consistent relationships exist between pediatric and adult anxiety. Infants who react negatively to novelty tend to become toddlers who avoid social novelty (Fox, Henderson et al., 2005). Toddlers displaying this profile have been termed 'behaviorally inhibited' (Kagan, 1994). Behavioral inhibition, in turn, predicts two-to-four fold increased risk for pediatric anxiety disorders (Perez-Edgar & Fox, 2005), and children with SOPH, SAD, or GAD, in turn, have been shown to face two-to three-fold increased risk for adult anxiety disorders (Pine, Cohen et al., 1998; Gregory et al., 2007). Finally, while longitudinal studies find strong within-person associations, family-genetic studies document equally strong cross-generational, developmental associations. Children born to parents with panic disorder or SOPH exhibit a two- to four-fold increased risk for behavioral inhibition, SOPH, SAD, or GAD (Merikangas, Avenevoli et al., 1999; Rosenbaum, Biederman et al., 2000; Pine et al., 2005).

Conflict of interest statement: No conflicts declared.

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Published by Blackwell Publishing, 9600 Garsington Road, Oxford OX4 2DQ, UK and 350 Main Street, Malden, MA 02148, USA

It remains unclear the degree to which such developmental relationships reflect the influences of genes or the environment. Available data suggest that anxiety disorders arise through complex pathways involving many causal factors, including both genes and the environment (Rutter, Moffitt et al., 2006). Thus, both manifestations of anxiety during childhood as well as relationships among pediatric anxiety and later psychopathologies are likely to reflect both the main effects of genes and the environment as well as gene–environment interactions.

*Specificity and prediction.* Two major questions emerge from this research. One set concerns specificity in outcomes. While behaviorally inhibited toddlers face high risk for anxiety, they also face elevated risk for major depressive disorder (MDD) (Caspi, Moffitt et al., 1996). Similarly non-specific associations with MDD emerge in longitudinal and family studies of older children (Pine, Cohen et al., 1998; Weissman, Wickramaratne et al., 2005). Some work documents specific associations among behavioral inhibition, pediatric SOPH, and adult SOPH (Pine, Cohen et al., 1998; Perez-Edgar & Fox, 2005). Moreover, family studies find that pediatric SAD but not pediatric SOPH aggregates with parental PD (Biederman, Faraone et al., 2001). Nevertheless, other associations appear less specific. Thus, pediatric SAD, SOPH, and GAD all show strong associations with parental MDD (Biederman, Faraone et al., 2001; Lieb, Isensee et al., 2002), whereas pediatric GAD prospectively predicts risk for adult MDD and anxiety disorders (Pine, Cohen et al., 1998; Gregory et al., 2007). In general, the data provide stronger support for specificity in SOPH and SAD than GAD. In fact, data on comorbidity, family-genetics, and outcome raise questions on the status of GAD as a discrete entity altogether.

Hence, these findings illustrate the principle of heterotypic continuity: infants showing undifferentiated distress reactions to novelty become toddlers with anxiety in social settings. These toddlers become children with anxiety in diverse settings, who mature into adults with anxiety, MDD, or both conditions. Major questions, however, remain concerning how it is that one group of at-risk children develop MDD while another develop anxiety.

A second set of related questions concerns factors that interact with underlying risk. Asymmetry emerges in longitudinal studies, which find that a minority of at-risk individuals ultimately manifests persistent disorders. For example, no more than 50% of inhibited children develop pediatric anxiety disorders (Perez-Edgar & Fox, 2005); approximately 50% of adolescents with anxiety disorders manifest adult psychopathology (Pine, Cohen et al., 1998; Gregory et al., in press). Nevertheless, adult mood or anxiety disorders are much more common in at-risk, relative to low-risk, juveniles. Thus, while absolute risk for poor adult outcome in at-risk children is

moderate, the risk is much higher than in low-risk children. At-risk status constrains but does not predetermine adult outcome in a deterministic fashion, raising questions about mechanisms that lead an underlying diathesis to either be manifest or remain silent.

*Alternative frameworks.* Failure to answer these questions may relate to the fact that clinical perspectives rarely capitalize on findings from neuroscience, which elucidate mechanistic understandings of fear-related behaviors. The hope had been that categories derived from clinical description would ‘carve nature at its joints’, identifying syndromes closely linked to brain dysfunction. Because this hope has not been realized, alternative frameworks are needed. Work on anxiety provides opportunities for grounding classification in neuroscience.

### *Affective neuroscience*

*Fear conditioning.* Research in neuroscience precisely delineates a neural circuit engaged by threats, stimuli that organisms put forth effort to avoid. The amygdala, a bilateral temporal lobe collection of nuclei, plays a central role in organizing threat responses, as classically studied in fear conditioning, the process whereby a neutral conditioned stimulus (CS+) is paired with an aversive unconditioned stimulus (UCS). Following conditioning, the CS+ comes to elicit neural reactions, psychological processes, and behaviors previously associated with the UCS.

Conditioning causes changes with clear cross-species comparability, contributing to detailed analysis of brain–behavior associations (Davis, 1998; LeDoux, 2000; Davis & Whalen, 2001; Phelps, 2006). The amygdala is necessary for CS+–UCS learning, although long-term memory of associations may be stored elsewhere. The amygdala facilitates learning by regulating attention allocation to the CS+, a function engaged during learning about both positive and negative-valence stimuli (Davis & Whalen, 2001; Holland & Gallagher, 2004; Blair, Mitchell, & Blair, 2005).

The timing of events during conditioning has been delineated with millisecond-level accuracy, such that amygdala engagement has been demonstrated immediately following CS+–UCS pairings and CS+ presentations (LeDoux, 2000). Over time, this process may support other forms of learning that engage extra-amygdala circuitry (Blair et al., 2005). For example, modulation of CS+–UCS learning occurs through interactions with the hippocampus and prefrontal cortex (PFC), particularly ventral and medial PFC expanses (Phelps, 2006). Specifically, CS+–UCS representations can be tied to specific spatial or temporal contexts, requiring hippocampal and PFC engagement, respectively. Particular interest has emerged in the role of PFC–amygdala circuitry in extinction, a process where CS+–UCS representa-

tions are tied to specific temporal contexts. As outlined below, development of fear-related behaviors may reflect the degree to which context-constrained threat representations change with maturation.

*Heterogeneity in threat processing.* Distinct threats engage distinct circuitry. This reflects threat content: conditioned cues engage neural components distinct from those engaged by innate threats, whereas threats from con-specifics engage different circuits than threats from predators or separation (Davis, 1998; Panksepp, 1998; Nestler & Carlezon, 2006). Similarly, distinct circuitry supports distinct learning processes. Learning to associate cues with punishers (stimulus-reinforcement learning) engages circuitry distinct from that engaged when learning to make the correct choice to minimize punishment (stimulus-response learning) (Blair et al., 2005).

Dissociable circuitry may explain why it is that an organism can show heightened fear to an isolated class of threat. Manipulations can produce restricted alterations in narrow aspects of the threat response (Blanchard, Griebel, Henrie, & Blanchard, 1997; Amaral, 2003; Bauman, Lavenex et al., 2004; Gross & Hen, 2004; Weisstaub, Zhou et al., 2006). Given cross-species parallels, the dissociable nature of individual differences in fear-related behaviors among rodents and non-human primates suggests the importance of encouraging efforts to validate distinct subtypes of anxiety disorders.

*Development.* Studies in rodents and non-human primates demonstrate the uniquely plastic state of the immature fear circuit. Early-life influences constrain the range of fear behaviors manifest throughout life, such that early life influences shape an underlying diathesis for threat responding (Gross & Hen, 2004). Much like in humans, where pediatric anxiety constrains but does not determine adult outcomes, an early-life diathesis may not manifest in later-life overt behavior, depending on other developmental influences (Francis, Diorio et al., 2002). Data in animal models suggest that adult anxiety reflects influences of genes and environments on fear circuitry, with the timing of these influences producing heterogeneous outcomes across individuals. For example, amygdala lesions in adult non-human primates produce broad reductions in fear, whereas the same lesions in childhood produce *increases* in social fear but reductions in other forms of fear (Amaral, 2003; Bauman, Lavenex et al., 2004).

Efforts to integrate developmental work on fear in rodents, non-human primates, and humans might benefit from an explicit research focus on specific components of distributed circuitry engaged by threats. Two anatomical regions appear worthy of specific focus. First, as noted above, the amygdala plays a crucial role in threat response behavior by regulating attention allocation. The intrinsic struc-

tural integrity of this region matures early in primates, suggesting that capacity for adult-type amygdala responses emerges well before adolescence (Pine, 2003). Nevertheless, cortical-amygdala connections undergo refinements over a more protracted developmental period. While developmental changes in connections with posterior temporal association cortex have been documented most comprehensively, the amygdala also shows extensive connectivity with the PFC (Pine, 2003). Thus, the PFC represents the second brain region worthy of focused research on developmental aspects of the threat response.

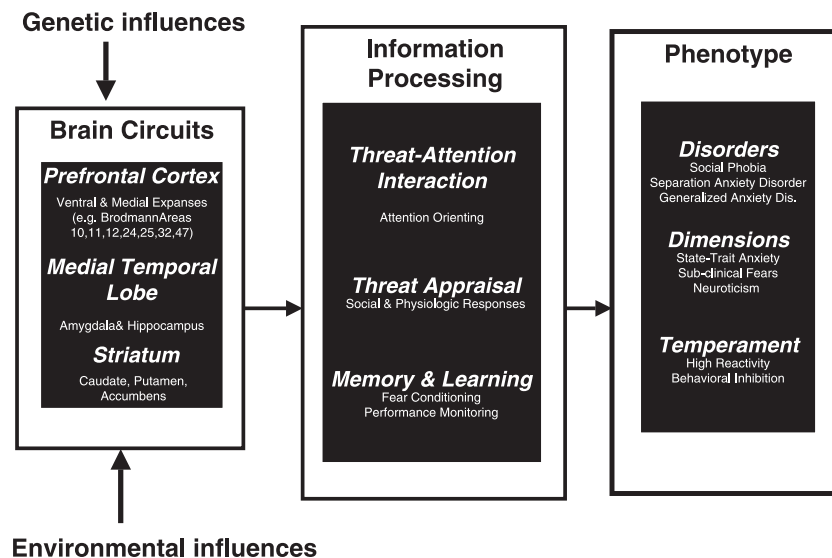
Comprehensive review of PFC anatomy and function can be found elsewhere (Fuster, 2001; Miller & Cohen, 2001; Blair et al., 2005). Briefly stated, while some disagreement persists concerning specific details, based on extrinsic connections and intrinsic cytoarchitectonics, most theoreticians recognize three basic PFC components: dorsolateral PFC (DLPFC), medial PFC, and ventral PFC, three regions that can be further subdivided. Thus, medial PFC also can be divided into dorsal and ventral components, as well as into a posterior expanse, encompassing the cingulate gyrus, and an anterior expanse, encompassing Brodmann's areas 9 and 10 (Picard & Strick, 2001; Amodio & Frith, 2006). Similarly, ventral PFC can be divided into orbito-medial and ventrolateral components (Ongur & Price, 2000).

Extensive amygdala connections exist with ventral PFC components as well as with ventral cingulate cortex specifically but not with DLPFC. These distinct anatomical connections with the amygdala are thought to account for the robust effects of ventral PFC lesions, particularly orbital/medial lesions, on emotional processes and decision-making. Finally, through interactions with the amygdala, distinct ventral PFC circuitry can support distinct aspects of emotional processes. For example, ventromedial PFC may be most prominently engaged when forming associations between neutral and motivationally salient stimuli. Ventro-lateral PFC may be engaged, in contrast, when these associations must be modified (Budhani, Marsh, Pine, & Blair, in press). PFC connectivity develops later than intrinsic amygdala connectivity (Pine, 2003). Thus, functional developmental changes in PFC-amygdala circuitry might manifest in humans in processes such as extinction, which require CS+–UCS associations to be tied to specific contexts.

## An information processing framework

### *Outlining a framework*

Clinical perspectives integrating data from neuroscience have emerged slowly, due to difficulty assessing parameters in humans that quantify anxiety disorder criteria in a fashion that maps onto



**Figure 1** The current framework. This displays relationships among functional aspects of brain circuits, psychological processes, and clinical phenotypes

constructs in neuroscience. Functions instantiated in neural circuits have been defined based on information processing-operations, as opposed to disorder criteria. Basic clinical integration might rely on a framework that maps relations between information processing operations and reports of distress or avoidance. Given that work in neuroscience dissociates correlates of overt behaviors and underlying diathesis, studies in humans will need to map correlates of both risk factors and overt anxiety disorders. Figure 1 illustrates this framework. Pathophysiologic explanations begin from the left side of the figure: genes and the environment influence circuitry that shapes threat responses. These effects do not map directly onto phenotypes but rather influence information processing. This framework delineates relevant psychological processes, depicted in the middle box, at a broad, general, conceptual level. As discussed below, these processes can be decomposed to generate more specific predictions that can be tested based on current understandings of brain-behavior associations.

This framework adopts a broad perspective on phenotypes, viewed as early-emerging profiles manifest across diverse settings to yield between-subject differences. Thus, classifications of infants as 'high reactive' or of toddlers as 'behavioral inhibited' fit in this box, as do diagnoses of SOPH, SAD, and GAD. The framework remains agnostic on the continuous or categorical nature of clinical features, such that dimensional constructs also fit in this box. Given a focus on psychopathology, the current perspective emphasizes results for phenotypes, conceptualized as categories, reflecting either the presence of impairment, for a disorder, or reflecting extreme scores, for dimensions. However, the true nature of phenotypes as categories or dimensions only will be revealed based on the underlying

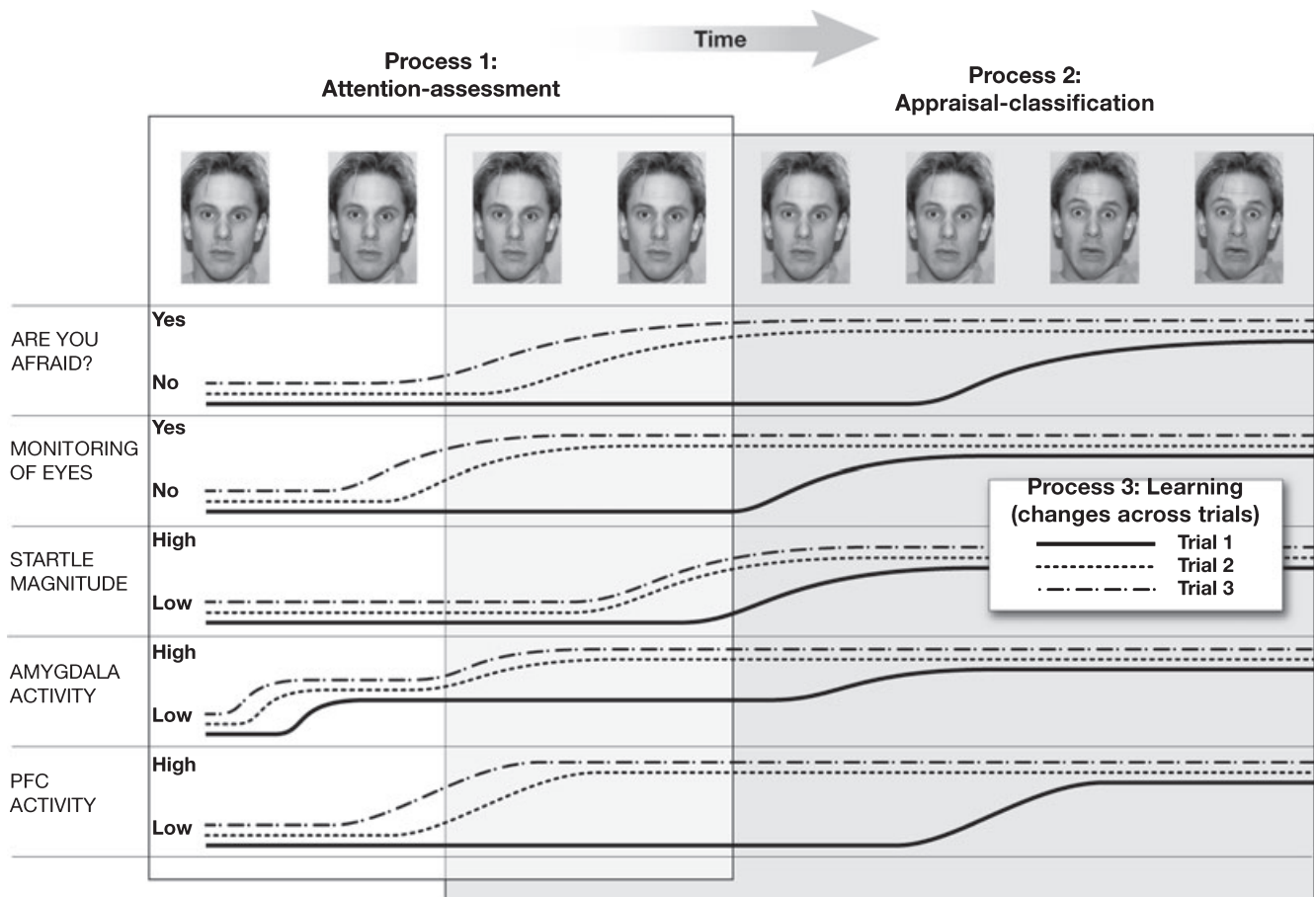
relationships with pathophysiology, which may be either continuous or categorical.

Application of this framework requires information processing quantification in a fashion that maps simultaneously onto measures of brain function and clinical anxiety. This is possible through paradigms that use experimental manipulations to generate on-line assessments of relevant processes. Such paradigms expose children of various phenotypes to salient emotional events as children are asked to perform a cognitive task. In practice, most work examines children aged nine or older, due to methodological complications in work with young children. As a result, the current review highlights work with this age group.

### *Three specific information processing functions*

Three groups of processes relevant to pediatric anxiety can be distinguished, each providing unique insights on clinical dimensions. (1) Attention-assessment processes provide insights on factors associated with broadly conceptualized anxiety disorders, as a group. (2) Appraisal-classification processes provide insights on factors more narrowly linked to specific anxiety disorders. (3) Learning-related processes provide insights on factors that might distinguish mood and anxiety disorders both from each other and from healthy states. For each process, threats are known to influence behavior and brain function in an adaptive fashion among healthy individuals. In anxious patients, processing biases reflect elicitation of fear-relevant processing in contexts where elicitation is maladaptive and not found in healthy individuals.

Figure 2 presents a schematic for a hypothetical paradigm that engages these processes. In each trial for the paradigm, research participants view pictures of an individual, as depicted along the top of the



**Figure 2** A theoretical experimental paradigm. One trial is depicted across the top of the figure, whereby research participants are presented with photographs of an individual. Initially, these photographs depict neutral emotion, but the emotion in the photographs gradually changes to become fearful. Anxiety-related attention processes are engaged very early following stimulus presentation, as indicated by the label 'Process 1'. Research participants indicate their level of fear during the task, providing an index of threat appraisal processes, as indicated by the label 'Process 2'. Learning occurs with repeated presentation of faces across trials, as indicated by the label 'Process 3'

figure. Over time in a single trial, the expression on the individual's face gradually morphs to depict fear. With ensuing trials, participants learn to anticipate these changes. The research participant reports on experienced levels of fear, as depicted in hypothetical data below the photographs, with other data being depicted in other graphs.

A few aspects of Figure 2 are particularly relevant for integrative research. First, this task relies on facial photographs to engage threat-relevant information processing functions. Considerable work uses facial stimuli, given strong cross-cultural and developmental parallels in responses to faces. Face-emotion displays appear to engage an evolutionary conserved set of core neural and psychological processes in humans (Haxby, Hoffman et al., 2002). Second, for illustrative purposes, the hypothetical task simultaneously attempts to engage three suites of processes. In actuality, most experimental tasks focus on a narrow range of processes, given methodological constraints on task design. Finally, subjects are monitored through multiple information streams, and different streams show distinct time-related changes, which each may show distinct

associations with specific brain regions or specific phenotypes.

**Attention–threat interactions**

*Quantifying processes.* Given the brain's computational limitations, humans possess insufficient neural resources to extract all information from stimulus arrays. To solve this problem, processes termed 'attention' modulate perception. In one key model (Desimone, 1998; Pessoa & Ungerleider, 2004), features of stimuli compete for neural resources, and this competition is adjudicated by two sets of processes. One set responds to intrinsic stimulus features, independent of organism-specific features. Stimuli conveying threat-related information show an enhanced capacity for consuming attention resources, independent of goal demands. Another set relates to features of the organism, independent of stimulus features. Stimuli corresponding to specific threat-related concerns show an enhanced capacity for consuming attention resources. In the hypothetical paradigm shown in Figure 2, these attention processes might be reflec-

ted in eye-movement scanning around eye regions when facial photographs depict fear.

The current conceptualization also decomposes attention into more elementary components reflected in dissociable behaviors. These behaviors include the orienting of attention towards or away from specific stimuli, the maintenance of an aroused state, and the regulation of attention under states of competing goal demands. Because much of the work relating attention and anxiety focuses on aspects of attention orienting, using variants either of the Posner orienting or dot-probe paradigms, the current conceptualization focuses selectively on attention orienting.

In attention orienting tasks, threat-related stimuli are presented in spatially delimited locations, and subjects identify targets that replace threat-related stimuli, appearing either proximal or distal to the stimuli. Based on patterns of responding, the degree of attention capture can be inferred. Similarly, other research examines the degree to which threat content captures attention by interfering with a subject's ability to perform other tasks, although this research considers threat content effects both on orienting as well as attention regulation. For example, in the emotional Stroop and related paradigms, bottom-up capture interferes with color- or object-labeling tasks. Each of these paradigms probes the degree to which threat content in stimuli shows the capacity to alter an individual's focus of attention, as typically reflected in reaction time.

More than 150 independent empirical studies examine the relationship between aspects of orienting and anxiety (Williams, Mathews et al., 1996; Mogg & Bradley, 1998; Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & van IJzendoorn, 2007). This work shows that threat-related information exerts greater influences on orienting in individuals with anxiety disorders or high scores on anxiety scales, relative to non-anxious peers. Extreme threat modulates attention orienting in all humans, but the threshold for mild threats to influence orienting in anxious subjects is lower than in non-anxious subjects. From this perspective, a threat-relevant process is elicited in patients in a context where no such process is elicited in healthy individuals. The nature of this bias suggests that information processing functions adaptive in some circumstances occur in inappropriate contexts among patients with anxiety disorders. While these findings represent some of the best-replicated associations in research on human anxiety, the magnitude of the effect size in these studies is no more than moderate. Three major questions emerge concerning the nature of associations between individual differences in anxiety and information processing functions, including orienting.

*Core questions: timing, disorder-specificity, and risk.* First, questions emerge on the pattern and

timing of attention orienting perturbations, conceptualized both over brief time scales and the time scale of development. For brief time scales, Mogg and Bradley suggest that perturbations vary as a function of threat intensity and exposure duration (Mogg & Bradley, 1998; Garner, Mogg, & Bradley, 2006). For mild threats, anxious individuals tend initially to automatically allocate attention towards threats, whereas healthy individuals typically show no threat-related modulation or sometimes even a tendency to avoid mild threats. However, as threat intensity increases, anxious individuals may show a tendency to avoid threat, following their initial automatic orienting towards it. In this instance, later attention responses, associated with threat avoidance and escape, compete with initial, automatic vigilant-monitoring tendencies. Similarly, as threat intensity increases, non-anxious individuals show bias in initial orienting, as threat value of stimuli cross the threshold for engaging vigilance. From this perspective, initial orienting towards threat might be conceptualized as a form of initial, automatic reactivity, whereas subsequent avoidance might be conceptualized as a form of regulation.

In terms of developmental time scales, some preliminary evidence finds maturational differences in the threshold for displaying these attention-orienting patterns to threats. For example, preliminary work finds that healthy adolescents orient towards threat on paradigms where healthy adults show no bias and that anxious adolescents display avoidance on paradigms where anxious adults display vigilance (Monk et al., 2006). This suggests that maturation involves an increase in the threshold for threats to influence orienting. Nevertheless, the nature and time course of such changes remain unclear: it remains unclear under which precise circumstances, during which precise timing parameters, and at which specific developmental periods anxiety is associated with attention orienting towards or away from threat.

Second, it remains unclear the degree to which attention biases map onto nosology. While some work documents disorder-specific biases in adults (Williams, Mathews et al., 1996), the weight of the evidence does not support this view (Bar-Haim et al., 2007). Threat-related attention orienting biases typically do not occur in MDD, but they do occur in virtually all forms of anxiety (Monk & Pine, 2004; Monk et al., 2006). Moreover, biases do not appear specific to clinically relevant threats. For example, orienting biases for social threats occur both in patients with SOPH and also in patients with anxiety about non-social circumstances (Mogg & Bradley, 1998; Monk & Pine, 2004). Thus, orienting biases relate to anxiety disorders as a dimension or class of syndromes, characterizing individuals in terms of general risk for or presence of an anxiety disorder.

Finally, it remains unclear the degree to which orienting relates specifically to underlying risk, as

opposed to overt expression of anxiety. While many theories view orienting biases as risk factors, data inconsistently support this view. For example, these biases tend to disappear following successful treatment, inconsistent with trait effects (Williams, Mathews et al., 1996). Moreover, the biases are quite plastic, altered by brief training exercises (MacLeod, Rutherford et al., 2002; Monk, Nelson et al., 2004). On the other hand, some evidence suggests that biases predict individual differences in emotional responses to stressors (MacLeod, Rutherford et al., 2002). Moreover, biases are expressed in both child and adult anxiety disorders, suggesting that they emerge early. Therefore, while support for both trait and state influences emerges, it remains unclear the precise manner in which orienting biases relate to anxiety.

*Hypotheses.* Three hypotheses emerge from this work. First, attention orienting biases are hypothesized to occur in all anxiety-related phenotypes, including specific anxiety disorders, inhibited temperaments, and sub-clinical elevations on anxiety scales. Second, from the developmental perspective, immature anxiety-related orienting biases are expected to emerge early in life, support the development of other anxiety-related biases, and change with development. Thus, in children, relative to adults, lower threat levels are expected to engage orienting; with increasing threat, the threshold for avoidance is expected to be lower in juveniles. These patterns are expected to reflect the plastic state of children's threat-processing circuitry. Finally, contextual factors are hypothesized to moderate the relationship between attention and risk. While threat bias is expected in at-risk/unaffected individuals, data on plasticity suggest that this bias manifests primarily under stress and associated increases in ongoing anxiety, such that stress exposure potentiates threat bias and symptomatic expression in at-risk/unaffected youth. Thus, the relationship between ongoing anxiety and threat bias would be expected to be strongest in individuals who also show an underlying diathesis for anxiety, based on family-genetic or temperamental factors. This early-manifesting orienting bias is expected to influence risk by ultimately shaping a second cognitive process: appraisal bias.

### *Threat appraisal*

*Quantifying processes.* Biases in attention orienting are engaged rapidly, reflecting immediate classification of stimuli as worthy of approach or avoidance. Attention-related difference in immediate classifications is reflected in orienting biases manifest within milliseconds of stimulus exposure. Such classification is considered 'implicit', in that it is minimally influenced by an organism's goals. However, with more extended exposures, organisms

perform more elaborate classifications of a stimulus's potential for harming.

This later aspect of classification involves explicit processes that *are* heavily influenced by an organism's current goals. The early, automatic, implicit classification occurs iteratively, in parallel, with this later, more elaborate, explicit classification, such that each of the two classification processes influences the other. The term 'appraisal bias' refers to individual differences in the later output of the explicit classification process and the associated response to threats. In this conceptualization, an 'appraisal' refers to a relatively narrow construct involving an interpretation of an event in terms of its meaningfulness for the individual. This represents a somewhat different use of 'appraisal' than in social psychology. Specifically, in the current context, the appraising organism considers the degree to which stimuli are relevant for well-being based on stimuli's capacity to effect the organism's goals (Sander, Grandjean et al., 2005). Moreover, the process of appraisal engages efforts to adjust to stimuli, which, when appraised as threatening, reflect aspects of defensive responding (Scherer, 2001). An appraisal bias indicates that an individual classifies as dangerous or threatening stimuli that most individuals classify as not dangerous or non-threatening. Appraisal bias can be indexed based on the verbal report of classification or based on a physiologic response on a defensive reflex.

Processes engaged during appraisal are linked to attention, given that the later, more elaborative aspects of classification are influenced by careful assessment, a process facilitated by attention, and by output of initial, automatic classification. Moreover, appraisal theory recognizes the process of threat classification as an iterative process, involving both early automatic classifications as well as more deliberative determination of stimulus significance and meaningfulness for the organism (Scherer, 2001). Relative to early attention processes, later appraisal processes allow more precise classification, whereby a detailed conclusion is reached and a series of more complex actions is initiated. For example, appraisal bias would be indexed by self-rated fear-state as well as by the amount of time required to make this rating. The tight, iterative relation between late appraisal and early attention manifests as correlations between the time required for explicit threat appraisal and the rating of threat intensity (Pine et al., 2005). Appraisal biases may, in fact, emerge through interactions with attention: children with attention bias are expected to learn to classify a broad range of stimuli as dangerous.

Human threat classification systems, as reflected in the subjective self-report and verbal labels applied to threats, involve complex, late-developing hierarchies, focusing with maturation on increasingly abstract and complex situations (Stattin, 1984; Ollendick, Yang et al., 1996). For example, young

children tend to classify specific objects, such as dangerous animals, as particularly threatening; adolescents tend to classify broad classes of conceptually related situations, such as those that elicit embarrassment, as particularly threatening. Moreover, growing complexities in adolescent social hierarchies increase the diversity of potential social threats and associated classification schemes, further implicating developmental changes in the manner in which threats are classified. Similarly, increasing cognitive skill affords adolescents opportunities to imagine and dwell on increasingly complex threats. Cross-cultural similarities suggest that maturation reflects intrinsically human processes. Finally, linguistic maturation provides novel means for regulating threat response. With development, increasingly complex schemes can be applied to label increasingly diverse classes of threats, reflecting greater understanding of threats. Increasingly precise labels reflect increasing capacity to predict threat occurrence and termination. Thus, a maturing organism is expected to use complex classification schemes for increasingly mature regulation of threat responses, suggesting that maturation in emotion regulation manifests in changing threat appraisal processes.

Such developmental changes in appraisal are likely to reflect developmental changes in associated neural architecture. While research implicates the amygdala in attention to threats, classification involves representation of complex stimulus features, instantiated in posterior temporal association cortex, and of stimulus salience, in ventral PFC. Thus, developmental changes in the classification of threats are expected to be reflected in changing threat appraisals, as represented in a circuit encompassing amygdala, posterior temporal cortex, and PFC.

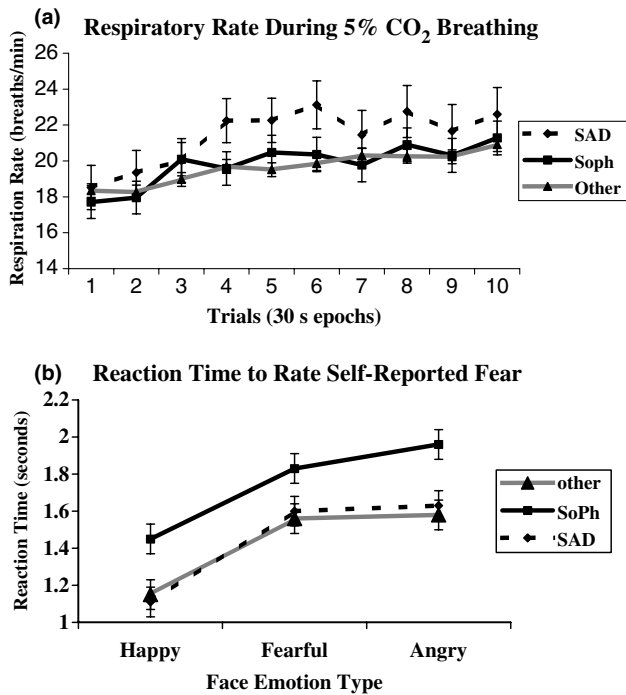
Threat appraisal processes are reflected in multiple forms of information. While verbal reports provide one form of information, a cession of behavior following stimulus presentation or response on a defensive reflex also might indicate classification of a stimulus as dangerous (Kalin, 2004). Defensive reflexes are indexed by autonomic, electromyographic, respiratory, and oculomotor measures (Mogg, Millar et al., 2000; Grillon, 2002; Pine et al., 2005; Pine, Klein et al., 2005; Garner et al., 2006). Complications in assessing threat appraisal emerge from the fact that diverse indicators may generate concordant or discordant classification. Considerable research links threat appraisal biases to clinical anxiety disorders. The magnitude of the effects can often appear quite large, with Cohen's standardized differences of .8 or greater (Monk & Pine, 2004), with both children and adults with anxiety disorders exhibiting a reduced threshold for classifying stimuli as dangerous. Similar questions exist concerning orienting and appraisal biases.

*Core questions: information streams, disorder-specificity, and risk.* One set of questions concerns the pattern of biases manifest across information streams and across development. Some research on anxiety disorders finds stronger appraisal biases on measures of verbal classification, as opposed to physiologic reflex responses (Merikangas, Avenevoli et al., 1999; Pine, Klein et al., 2005). In fact, in some scenarios, anxiety patients exhibit a heightened tendency to verbally classify situations as distressing at the same time that they exhibit a reduced physiologic response to the same situations (Cuthbert, Lang et al., 2003). In studies of other threat types, however, associations with anxiety have emerged for physiology but not reported fear (Grillon, Dierker et al., 1998). Moreover, it remains unclear the degree to which findings vary based on experimental demands. Explicitly asking patients to classify threats may engage processes not observed when patients passively view possible threats. Finally, in terms of development, considerable work documents changes in threat appraisal during typical development. However, it remains unclear the degree to which appraisal biases show developmentally stable or changing associations with pathological states.

A second set of questions concerns specificity across disorders. In this area, the data reveal tighter concordance with current nosology than for attention orienting. One relevant example emerges from research on pediatric SAD and SOPH. Figure 3 illustrates a double dissociation for these conditions, studied during exposure to two experimental threats.

SAD in children has been linked to panic disorder in parents, a condition associated with specific appraisal biases for respiratory threats, manifest as perturbations in respiratory physiology and heightened tendencies to feel afraid in smothering situations (Klein, 1993). Adolescents with SAD exhibit the same appraisal biases for respiratory threats found in adults with panic disorder (Pine, Klein et al., 2005). Figure 3a depicts one aspect of such an appraisal bias, manifest in a defensive physiologic reflex. Relative to healthy youth or youth with SOPH, youth with SAD exhibit brisker increases in respiratory rate during exposure to CO<sub>2</sub>-enriched air. This physiologic reflex response is paralleled by self-report data: SAD predicts increased reported fear and reported physiology symptoms in CO<sub>2</sub>-breathing. Thus, in markedly suffocating circumstances, all individuals would be expected to report fear and show marked respiratory changes. In minimally suffocating circumstances, however, only SAD but not healthy or SOPH individuals exhibit anxiety and marked respiratory changes, showing that anxiety disorders involve elicitation of threat-related processes in inappropriate contexts.

While youth with SOPH exhibit normal respiratory profiles to physiologic challenge, they exhibit



**Figure 3** Data for two experimental paradigms. These data appear in Pine et al. (2005a, 2005b). In the first paradigm, depicted in Figure 3a, patients with separation anxiety disorder (SAD) are shown to exhibit abnormalities in respiratory physiology, relative both to healthy peers and to patients with social phobia (SOPH). In the second paradigm, depicted in Figure 3b, patients with SOPH are shown to exhibit abnormalities in processes engaged while viewing faces and rating experienced fear. These abnormalities occur relative both to healthy peers and to patients with SAD

abnormal subjective appraisal responses to social threat. This finding is consistent with data in adult SOPH, which is associated with appraisal biases for social threats, manifest as avoidance and heightened fear in social situations. Adolescents with SOPH, but not adolescents with SAD, exhibit a threat appraisal bias for social stimuli, manifest as a prolongation of reaction time when monitoring one's level of fear induced by viewing facial photographs (Pine et al., 2005). Figure 3b depicts this finding in the same individuals used to display findings in Figure 3a. Again, these data reflect biases rather than qualitative differences: elevated anxiety rating and increasing focus on internally experienced anxiety occurs among healthy adolescents during highly stressful social interactions, but the engagement of threat-related processes occurs at lower thresholds in adolescent SOPH. Finally, available research relies on relatively indirect threats in SOPH, such as facial photographs. One would predict more extreme appraisal bias in the context of real-world social interactions in SOPH.

Despite this evidence of specific appraisal biases, signs of non-specificity emerge in other work. For example, youth with various anxiety disorders or those scoring high on anxiety scales show a height-

ened tendency to classify ambiguous stories as threatening (Muris, Luermans et al., 2000). Some evidence suggests that nosologically specific appraisal biases occur upon direct exposure to particular threats but that nosologically non-specific biases emerge when anticipating exposures to impending threats. For example, while pediatric SAD but not SOPH is associated with heightened anxiety during CO<sub>2</sub> breathing, pediatric SAD and SOPH both show heightened anxiety while anticipating CO<sub>2</sub>-exposure (Pine, Klein et al., 2005).

Third, it remains unclear if appraisal biases are risk factors for anxiety in unaffected children, as opposed to correlates of manifest anxiety. The most comprehensive effort to disentangle this issue relies on studies in offspring born to parents with panic disorder (Merikangas, Avenevoli et al., 1999; Pine et al., 2005; Pine, Klein et al., 2005). In general, this work finds that at-risk/unaffected adolescents exhibit a reduced threshold for classifying as dangerous a broad range of threats. However, at least for some disorder-specific threats, such as respiratory threats in SAD, the threshold for classifying a threat as dangerous is even lower in patients with overt disorders than in at-risk/unaffected individuals (Pine et al., 2005; Pine, Klein et al., 2005). Thus, the transition from at-risk/unaffected to affected status may involve development of heightened appraisal bias for specific threats, emerging against a background of mild hypersensitivity to diverse threats. At-risk children who remain healthy may mold this background of broad hypersensitivities by successfully learning to differentiate actual from potential threats.

Finally, different threats may show distinct associations with risk factors as opposed to overt disorders. For some threats, at-risk/unaffected individuals and at-risk/affected individuals exhibit the same bias, relative to low-risk/affected and low-risk/unaffected individuals (Grillon, Dierker et al., 1998; Pine et al., 2005). For other threats, associations appear additive, such that at-risk/affected individuals show the highest level of bias, with at-risk/unaffected or low-risk/affected individuals showing intermediate levels, relative to low-risk/unaffected individuals (Merikangas, Avenevoli et al., 1999; Pine et al., 2005; Pine, Klein et al., 2005).

**Hypotheses.** Three hypotheses emerge from this work. First, specific appraisal biases occur in specific disorders. While data dissociate SOPH from SAD, one would expect similarly specific biases in other pediatric anxiety disorders. Second, developmentally, early-life orienting biases are expected to predict emerging appraisal biases in subjective self-report and explicit verbal assessment of threat, which undergo age-related changes but also show heterotypic continuity. Thus, reticence in a toddler, experienced when attending a play date, is expected to predict anxiety in an adolescent, meeting new

classmates. Similarly, such adolescent anxiety is expected to predict anxiety in an adult making a business presentation. Trajectories are expected to reflect the degree to which at-risk children learn contexts under which to classify stimuli as dangerous. Finally, risk for anxiety is expected to involve both disorder-specific and cross-disorder biases. Risk for and expression of specific disorders may manifest with direct threat exposure, whereas general risk may manifest when anticipating exposure to a range of threats. An appraisal bias during threat anticipation also may represent a specific feature of GAD, in particular, accounting for the broad associations between GAD and other anxiety disorders.

### *Memory and learning*

While attention and appraisal biases manifest with initial threat exposures, memory or learning processes quantify adaptations following exposure. At a broad, general level, memory and learning is reflected in change over repeated presentations. Repeated face presentations in Figure 2, for example, lead subjects to anticipate changes in emotional expression, with shifts in responding: subjects learn to treat neutral stimuli as dangerous, based on pairings with emotion photographs (Lau & Essing, in press). One particularly important future avenue may involve explorations of the manner in which learning alters attention-orienting and appraisal biases. The above-noted age-related changes in these biases may reflect learning-related influences.

As with attention and appraisal, learning and memory represent complex high-level processes that can be decomposed into elementary processes to be studied in detail. While pediatric anxiety shows some relationship with memory and learning, no learning or memory paradigm reveals consistent associations with pediatric anxiety disorders. As a result, this area is reviewed in less detail than attention orienting or appraisal. In terms of more elementary learning-related processes, two specific areas have been studied in some detail: fear conditioning and conflict monitoring. Findings in anxiety for these two areas are briefly discussed.

Fear conditioning represents the best-studied learning-related phenomenon in the anxiety disorders. This process examines the degree to which an organism learns to associate a neutral CS+ stimulus with a dangerous UCS stimulus. While many theories suggest that anxiety patients' proficiency at fear conditioning accounts for their clinical state, available data show inconsistent relationships, with most studies examining adults (Lissek et al., 2005). For example, fear conditioning abnormalities in anxiety disorders emerge for simple cue conditioning but not for studies that use both CS+ and CS- stimuli. Some view such data as consistent with anxiety-related perturbations in classifying threats, rather than in tendencies to show enhanced condi-

tioning (Bouton, 2002; Grillon, 2002). Perspectives on extinction support this view. Extinction requires learning new associations with formerly dangerous CS+ stimuli, which are reclassified as safe in the new context, experienced without UCS (Bouton, 2002). Difficulties during extinction have been attributed to difficulties with stimulus classification (Grillon, 2002). Consistent with this possibility, manipulations targeting these difficulties might treat anxiety symptoms by facilitating extinction (Ressler, Rothbaum et al., 2004).

Inconsistent associations emerge for other learning indices. For example, while the weight of the evidence finds normal declarative memory for emotional material in anxiety, consistent evidence of emotion-related memory abnormalities emerges in MDD (Roberson-Nay, McClure et al., 2006). Interestingly, evidence finds dysfunction in declarative memory for neutral information in pediatric anxiety but not MDD (Vasa, Roberson-Nay et al., 2007).

In terms of conflict monitoring, recent work relevant to learning perturbations in pediatric anxiety focuses on performance of motor-response tasks, which lead subjects to adjust behavior over time. In this work, subjects typically engage in moderately difficult stimulus-response tasks, requiring either relatively subtle classification of non-emotional material or selection of a rapid response to one or another stimulus. When subjects face conflicts, performance-monitoring processes enable subjects to minimize errors over time (Forbes et al., 2006; Ladouceur, Dahl, Birmaher, Axelson, & Ryan, 2006). These processes register the occurrence of conflicts and facilitate behavioral adjustments, particularly when conflict is elevated. For example, following a punished error on a manual reaction-time task, subjects may slow their responses on subsequent trials. Increasing conflict augments performance monitoring, with pediatric anxiety predicting enhanced responses to conflict (Fox, Henderson et al., 2005; Ladouceur et al., 2006). Nevertheless, minimal work examines pediatric anxiety's association with fear conditioning or performance monitoring.

## **Neural structures engaged during information processing**

### *The nature of neuroscience data*

The strength of this framework lies in the fact that relevant information processing functions are examined based on neuroscience literature. This final section delineates the manner in which orienting, appraisal, and learning, the three processes illustrated in Figure 1 and 2, have been linked to brain function. In the current framework, phenotypes reflect differences in brain function that affect underlying information processing. The effects can

manifest in overt behavioral deviance or in aberrant neural engagement, with behavior appearing superficially intact. Despite the superficial appearance, in both instances, differences in brain function determine phenotype by perturbing information processing functions.

An example illustrates this principle. Alzheimer's disease causes amnesia and deficient medial temporal lobe function. Risk for the disease is manifest by abnormal medial temporal lobe engagement, even when memory encoding superficially appears intact (Bookheimer, Strojwas et al., 2000). With more sensitive assessments of behavior in this context, however, one also would expect to observe perturbed memory encoding, even in unaffected/at-risk subjects. Nevertheless, a relatively insensitive study of memory encoding in risk for Alzheimer's disease, acquiring no data on neural function, might be insensitive to process associated with risk. The same study acquiring such data would detect risk-related neural dysfunction. Similar findings emerge in research on associations among working memory, PFC function, and schizophrenia (Callicott, Mattay et al., 2003). Anxiety disorders are hypothesized to result from biases in orienting, appraisal, and learning, associated with deficient PFC, medial temporal lobe, and striatal function. Risk should manifest as abnormal neural engagement during such tasks, even in the face of task performance that appears superficially normal. A major goal should be to delineate the manner in which information processing patterns associated with anxiety map onto specific brain functions, both in typical and atypical development.

### *Structural vs. functional imaging*

Structural brain imaging also bears on neuroscience. Studies of patients with brain lesions implicate damage to specific structures in specific functional deficits (Drevets, 2001; Phelps, 2006). Accordingly, one might expect psychiatric patients to show structural changes in regions where frank brain injury in neurology patients perturbs clinically relevant processes. Similarly, changes in brain structure might reflect the chronic effects of repeated engagement of specific circuitry, in a fashion that leads to either compensated or perturbed function. Such changes could emerge through the effects of genes or the environment. Indeed, data in neurologically intact adults with various mood or anxiety disorders and their risk factors find evidence of structural defects in the amygdala, hippocampus, medial and ventral PFC (Drevets, 2001; Rauch, Shin et al., 2003; Pezawas, Meyer-Lindenberg et al., 2005).

While structural data broadly implicate circuits in behavior, they provide limited insights on mechanism. An overly simplified but illustrative example clarifies these limits. Structural injury to a brain

region may disrupt function, perturb information processing, and precipitate a disorder. This would lead one to hypothesize reduced brain volumes in relevant structures among patients with specific psychiatric disorders. Alternatively, the threshold for engaging a specific process may be altered in at-risk individuals, either through stress or the effects of genes. This change may lead to regional structural hypertrophy and onset of a disorder. Based on these data, one would expect disorder-associated *increases* in a brain structure.

This difficulty is illustrated in work on pediatric anxiety disorders. Two studies examine structural integrity of the fear circuit. Both found perturbed amygdala structure, but one found increased (De Bellis, Casey et al., 2000) and the other found decreased amygdala size (Millham et al., 2005). These problems may be addressed by acquisition of functional data. Activity in a circuit can be linked with clinical indices to clarify which of the above two scenarios most plausibly accounts for associations between perturbed information processing and disorders. Nevertheless, understandings of brain structure-function relationships continue to undergo rapid development. As a result, definitive insights on mechanisms remain elusive.

As reviewed above, basic research delineates neural circuits engaged by threat presentation. Even in healthy adults, the best-studied population, it remains unclear when to expect maximal engagement of these circuits during brain imaging, i.e., based on which conditions, by engaging which cognitive processes, performed during which specific threat exposures. While brain-imaging studies in juveniles document engagement of relevant circuits, these studies also suggest that circuits remain immature well into adolescence. Given the many questions, this final section summarizes current controversies, based largely on data in adults, and briefly reviews results from studies most directly relevant for pediatric anxiety disorders.

Considerable imaging research examines adult anxiety and mood disorders. These studies provide an important backdrop against which to place studies in pediatric anxiety disorders by implicating specific neural systems in perturbed aspects of threat processing. Three conclusions emerge from this work.

First, amygdala as well as ventro-medial and ventro-lateral PFC hyper-activation occurs in adults with a range of mood and anxiety disorders. These include most consistently SOPH and MDD (Stein, Goldin et al., 2002; Phillips, Drevets et al., 2003; Rauch, Shin et al., 2003). Interestingly, this work supports distinctions between SOPH/MDD and either obsessive-compulsive disorder or specific phobia, where normal amygdala function occurs on paradigms sensitive to dysfunction in SOPH or MDD. Second, the degree to which specific cognitive processes modulate these findings has not been

examined. Thus, amygdala/PFC hyper-activation occurs to threats, viewed in the context of diverse non-emotional tasks, including passive viewing or focus on non-emotional aspects of threats. However, no studies have compared amygdala and PFC engagement in adult patients and healthy subjects across psychological tasks or during explicitly emotional tasks. Research is needed both in adult and pediatric populations on the degree to which threat circuit hyper-activation is modulated by task demands. Third, available research documents both state and trait influences and fear-circuit dysfunction in adult mood and anxiety disorders. Thus, effective treatments normalize hyperactivation in some studies, implicating state factors (Rauch, Shin et al., 2003). On the other hand, genetic factors influence fear-circuit function among adults free of psychopathology (Pezawas, Meyer-Lindenberg et al., 2005). Given these data, studies in pediatric anxiety disorders might focus on the conditions under which patients exhibit fear-circuit hyperactivity while also considering the impact of state and trait factors.

### *Attention–threat interactions*

Studies in healthy subjects and in patients with brain lesions implicate the amygdala in attention–threat interactions (Pessoa & Ungerleider, 2004; Phelps, 2006). These studies demonstrate a role for the amygdala in orienting; a role for PFC-modulation of amygdala function has been demonstrated in tasks where attending to threats competes with goal demands.

Considerable controversy persists over the precise conditions associated with amygdala engagement in healthy adults. Stimulus features clearly modulate engagement, as emotionally evocative stimuli engage the amygdala more consistently than neutral stimuli (Wager, Phan et al., 2003). Nevertheless, it remains unclear the degree to which stimulus valence as opposed to overall salience is key. Similarly, amygdala activity varies with task demands (Pessoa & Ungerleider, 2004). Nevertheless, amygdala engagement occurs on tasks using briefly presented degraded stimuli, where task demands cannot easily influence engagement (Dolan, 2002).

Brain imaging studies in healthy adults have begun to use attention orienting tasks on which anxiety disorder patients show perturbed behavioral performance. While these studies do document engagement of relevant circuitry, the precise conditions under which specific structures become engaged remain unclear. Only one brain imaging study, with functional magnetic resonance imaging (fMRI), used a threat-orienting task in youth (Monk et al., 2006). In this study, adolescents with GAD performing a threat-dot-probe task exhibited enhanced activity in ventrolateral PFC (VLPFC), a region that modulates fear and amygdala activation in animal models (Quirk & Gehlert, 2003). Consistent

with a regulatory role for this structure, greater VLPFC engagement predicted lower anxiety in patients. Finally, this study examined adolescents with GAD, a condition that predicts non-specific risk for many anxiety disorders. Further studies examining variations in VLPFC engagement, attention orientation, and anxiety symptom profiles may clarify factors that create broad predisposition for anxiety disorders.

*Hypotheses.* Associations between orienting bias and anxiety are hypothesized to reflect perturbations in amygdala–VLPFC circuitry. The amygdala is hypothesized to represent stimulus–reinforcement associations mediating this bias. Developmental and clinical differences in the amygdala on attention orienting paradigms are expected, reflecting a heightened sensitivity for amygdala engagement in children, relative to adults, and in anxiety patients, relative to healthy subjects. These differences are expected to manifest in orienting paradigms with briefly presented threats or with other features that facilitate amygdala engagement. In this instance, one would expect positive correlations between amygdala activity and anxiety levels.

In the context of orienting, VLPFC is hypothesized to allow flexible deployment of attention, so that appropriate goal set is maintained despite threat interference. From this perspective, VLPFC engagement regulates amygdala activity, with greater VLPFC activation required to perform tasks where attention must be redirected away from threat. Thus, one would expect no relevant between-group differences in orienting tasks involving no threat. At low threat levels, one would expect between-group differences in the amygdala but not VLPFC, whereas at higher threat levels, one would expect the converse.

### *Threat appraisal*

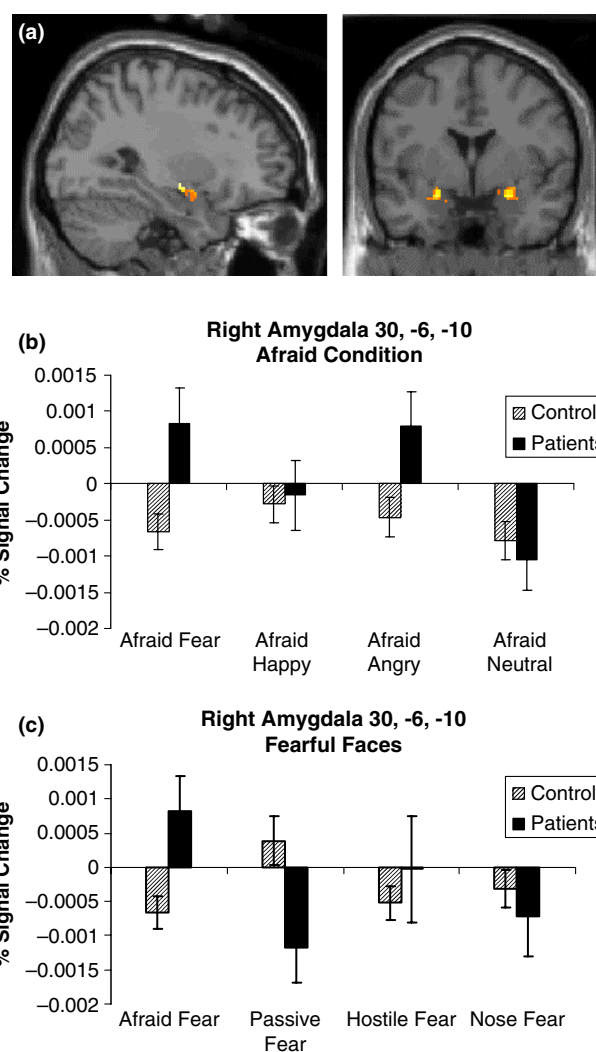
Presenting threats in brain imaging experiments consistently engages the amygdala as well as the ventral and medial PFC (Wager, Phan et al., 2003). However, it remains unclear which precise task demands maximize engagement of one or another fear circuit component both in healthy subjects and subjects with anxiety disorders. Considerable work examines engagement of brain regions associated with aspects of appraisal that extend beyond rapid, automatic classifications of threat-related stimuli. This work suggests that the medial PFC plays a particularly important role in performing appraisal explicitly requiring the monitoring of one's own emotional state (Amodio & Frith, 2006). This process is centrally related to determinations of meaningfulness, a key aspect of appraisal (Scherer, 2001). From the clinical perspective, the extreme distress associated with an anxiety disorder can be conceptualized as perturbed emotional-state monitoring. As a result, tasks that require subjects to actively

monitor emotional state during threat presentation provide a novel means for examining the role of PFC in anxiety and associated perturbations in threat appraisal.

For the amygdala, passive-threat viewing engages this structure in healthy adults and adolescents, with greater activation in adults with anxiety disorders, relative to healthy adults (Rauch, Shin et al., 2003). Performance of cognitive tasks reduces amygdala activation in healthy adolescents (McClure et al., 2007). Because it remains unclear which precise processes are engaged during passive viewing, unclear implications derive from these studies. Nevertheless, studies using passive-viewing tasks typically assume some engagement of threat-appraisal processes. Three fMRI studies used passive viewing tasks to examine the relationship between amygdala activation and pediatric anxiety, all three relying on block designs. This design is sensitive to psychological and associated neural processes engaged for relatively sustained time periods. While all three studies implicate the amygdala in pediatric anxiety, they leave unanswered questions concerning processes underlying the amygdala–anxiety relationship.

The first fMRI study documented enhanced amygdala activation to fear faces in pediatric GAD or panic disorder, as well as a positive correlation between amygdala activation and self-reported anxiety symptoms (Thomas, Drevets et al., 2001). The second documented enhanced amygdala activation during adulthood in formerly inhibited children (Schwartz, Wright et al., 2003). Of note, this study demonstrated enhanced activation to neutral novel faces, suggesting that perturbations in behavioral inhibition are associated with appraisal of novelty. The third fMRI study documented a positive correlation between sub-clinical anxiety symptoms and amygdala activation to fear faces in healthy adolescents (Killgore & Yurgelun-Todd, 2005).

A fourth study relied on event-related fMRI methods and experimental manipulations of task conditions. This design clarifies the degree to which appraisal biases might mediate the previously observed associations between pediatric anxiety and amygdala hyperactivity. Figure 4 displays data from this study (McClure et al., 2007). This study found that engagement of threat appraisal processes moderates the relationship between pediatric anxiety and amygdala activation. Specifically, the study found that adolescents with GAD but not healthy adolescents showed a facilitation of amygdala engagement, as well as ventral and medial PFC engagement, when making threat appraisals for facial photographs, as contrasted with events during which the same photographs were passively viewed. Figure 4 shows an enhanced activation in the amygdala among GAD adolescents only when making a threat appraisal judgment for angry or fearful faces but not when engaging other processes. These



**Figure 4** Amygdala activity in a group of adolescent patients with generalized anxiety disorder (GAD,  $n = 15$ ) and a group of healthy adolescents ( $n = 20$ ). Figure 4a presents a map that contrasts activity in the amygdala of GAD and healthy subjects for a contrast of viewing fearful faces versus happy faces, all viewed while performing a threat-appraisal rating. Figure 4b displays activity in the right amygdala while viewing fearful, happy, angry, and neutral faces. As shown, between-group differences emerge for fearful and angry faces, the two negative emotions. Figure 4c displays activity in the right amygdala while viewing fear faces across four attention conditions. As shown, between-group differences emerge only in the threat-appraisal attention state

data show that task demands constrain between-group differences in amygdala function. Moreover, consistent with a regulatory role for the PFC, enhanced PFC–amygdala coupling predicted a lower level of anxiety in adolescent GAD patients. Finally, the study used a paradigm derived from the task shown in Figure 3b, though the data in Figure 3b emerge from a study in at-risk adolescents, studied in their homes (Pine et al., 2005), whereas the data in Figure 4 emerge from affected adolescents, studied in an MRI scanner (McClure et al., 2007). Findings

from the two studies demonstrate the importance of integrating studies of behavior and brain function.

Notable parallels and discrepancies emerge across the two studies. In both, between-group differences only emerge during threat-appraisal tasks, providing support for positions implicating threat appraisal biases specifically in pediatric anxiety. However, in the behavioral study, differences were found in SOPH, but not SAD, and occurred for all face-emotion types; the study included too few subjects with GAD to examine findings for this group. In the fMRI study, on GAD, differences were found only for appraisal of negative face-emotions. Future work should contrast individuals with GAD, SOPH, and SAD. Based on longitudinal, family-genetic, and behavioral data in Figure 3, one would expect the patterns shown in Figure 4 to characterize individuals with SOPH and GAD but not individuals with SAD or MDD, in the absence of SOPH or GAD.

This prediction suggests that abnormal fear circuit engagement can be dissociated across specific anxiety disorders and MDD, during appraisal of particular threats. Other work in developmental psychopathology supports this idea, with probably the best example emerging for Williams syndrome (Meyer-Lindenberg, Hariri et al., 2005). This condition involves high degrees of pediatric anxiety manifest towards various situations, with the notable exception of social situations. This implicates developmental dissociations between brain systems associated with appraisal of social vs. non-social threats. Data from brain imaging experiments support this contention by finding stimulus-specific neural correlates: Williams syndrome patients show perturbed fear-circuit engagement during appraisal of non-social but not social threats.

*Hypotheses.* Like orienting biases, associations between appraisal biases and anxiety are hypothesized to reflect perturbations in amygdala-PFC circuitry. However, the nature of disorder-linked perturbations is expected to differ in orienting and appraisal. Medial and ventral PFC engagement is hypothesized to be crucial for stimulus classification, as occurs during appraisal, by integrating activity within posterior association cortices and the amygdala.

For orienting in anxiety patients, enhanced amygdala but not VLPFC engagement is expected for minor threats, with the converse for higher threats. In appraisal biases, the nature of amygdala-PFC activation also may vary based on threat levels, though in a different manner than for orienting. With minor threats, simultaneous PFC-amygdala engagement is expected during appraisal, such that one would expect increased amygdala activation in anxiety patients, in the context of correlated increases in PFC activation. With higher threats, however, inverse PFC-amygdala engagement would be expected, with the PFC regulating amygdala

engagement. This is consistent with Blair et al. (2005), where amygdala-antero-medial PFC engagement reflects active representation of stimulus-reinforcement associations, with stronger engagement in patients reflecting the enhanced salience of threat-related associations. In dorsal medial and lateral PFC, however, engagement reflects regulatory influences that counteract amygdala engagement (Budhani et al., 2007).

Of note, available imaging work on appraisal bias relies on relatively low-level threats, such as negative-valence facial photographs. One also would expect SOPH-related amygdala perturbation to more extreme threats, such as anticipation of real social interactions, with perturbations being driven by subjects' specific appraisal of events. Thus, positive-valence photographs, which most adolescents would appraise as appealing, might elicit enhanced amygdala activation in pediatric SOPH if contextual factors led such photographs to be appraised as threatening. For example, enhanced amygdala activation might emerge to photographs of smiling peers misperceived by the SOPH adolescent as derisive.

### *Memory and learning*

Brain imaging studies in adults consistently implicate the amygdala in various forms of learning (Phelps, 2006). This includes fear conditioning and memory encoding of highly aversive stimuli. For ethical reasons, it has been difficult to implement comparable studies among children and adolescents. No fMRI study has examined fear conditioning in children and adolescents. Memory for mildly arousing emotional stimuli appears more consistently perturbed in adult and adolescent MDD than in adult or adolescent anxiety. Consistent with these findings, a recent fMRI study demonstrated abnormal amygdala engagement in adolescent MDD but not anxiety disorders during emotional memory encoding (Roberson-Nay, McClure et al., 2007).

Studies of conflict monitoring present fewer ethical quandaries than studies of fear conditioning or aversive memory encoding. Research on conflict monitoring in healthy individuals focuses on engagement of fronto-striatal, more than amygdala-based, circuits by mapping brain regions engaged when subjects perform motor responses to obtain rewards. In this setting, events where expectations are violated lead to striatal engagement and fronto-striatal interactions through which the PFC ultimately comes to encode contexts under which specific actions are expected to predict specific rewards (Miller & Cohen, 2001). This aspect of fronto-striatal circuitry undergoes profound changes through adolescence (Galvan, Hare et al., 2006).

Given this view of fronto-striatal circuitry, coupled with prior behavioral data on anxiety and decision-making, anxiety-related differences in fronto-striatal engagement would be expected when individuals

anticipate performance feedback on motor-response tasks. Consistent with this possibility, emerging data implicate reduced threshold for fronto-striatal engagement in pediatric anxiety disorders or their risk factors. Thus, a recent evoked-potential study documents enhanced medial PFC engagement following error commission in anxiety disorders, consistent with data in behavioral inhibition (Fox, Henderson et al., 2005; Ladouceur et al., 2006). Moreover, fMRI data in formerly inhibited adolescents document enhanced striatal activation during reinforcer anticipation, further implicating enhanced striatal engagement in anxiety (Guyer, Nelson et al., 2006). Of note, between-group differences in the striatum emerged in the context of similar incentive-related increases in the amygdala, successfully dissociating amygdala and striatal correlates of risk for anxiety.

Data on neural correlates of memory and learning may differentiate both pediatric anxiety and MDD from healthy development. For threat-related appraisal and orienting biases, anxiety patients typically differ from both healthy subjects and patients with MDD, the latter two of whom do not differ. However, for some learning and memory tasks, both anxiety and MDD patients differ from healthy patients as well as from each other. Thus, research in this area may provide clues on mechanisms that account for the strong association between anxiety and MDD. Whereas studies of emotional memory show enhanced amygdala activation in MDD but not anxiety (Roberson-Nay, McClure et al., 2006), studies of fronto-striatal circuitry during decision-making show the opposite: pediatric anxiety is associated with enhanced, but pediatric MDD is associated with reduced, striatal activation (Forbes et al., 2006).

*Hypotheses.* Biases in learning and memory are expected to differentiate MDD and anxiety. During performance monitoring, between-group differences are expected within fronto-striatal executive attention networks. Similarly, when encoding emotional information, MDD but not anxiety is expected to predict enhanced amygdala engagement. Finally, anxiety but not MDD-related perturbation is expected during extinction, where difficulty distinguishing extinguished and non-extinguished CS+ reflects PFC dysfunction. These learning-related deficits are expected to impact orienting and appraisal biases, such that healthy development may involve successfully learning appropriate contexts in which to deploy threat-related information processing functions. Children at-risk for chronic anxiety are expected to exhibit early-life perturbations associated with amygdala-PFC-based orienting and appraisal biases, occurring in inappropriate contexts. Among at-risk youth who successfully learn the contexts under which to deploy threat-related processes, despite tendencies to engage threat-

related processes in safe contexts, anxiety ultimately would not be overtly manifest as a clinical phenotype. At-risk youth failing to modulate their underlying diathesis, by learning when to engage context-appropriate processes, would mature into adults with chronic anxiety. Thus, anxiety prevention may involve teaching skills at context discrimination, as opposed to overall reductions in threat response.

## Conclusions

The current review presents a framework for integrating clinical and basic perspectives on anxiety. The framework begins from the premise that development constrains the range of possible outcomes an organism can experience. Studies in animal models suggest that developmental events shape function in distributed neural circuits. The core of this framework involves implementing experimental research in the laboratory. Such research uses paradigms to engage suites of processes and associated neural architecture during exposure to various threat classes. Anxiety disorders are conceptualized as conditions that result from a collection of perturbations in such processes, with some relating to underlying risk, others relating to expression of any anxiety disorder, and a final set relating to more specific classes of disorder. At their core, these perturbations reflect failure to regulate threat-related information processing functions, such that elicitation of threat-appropriate processes occurs in settings that are minimally threatening for most individuals. Ultimately, knowledge on associations among brain function, these specific information processing functions, and phenotypes may lead to a nosology based in neuroscience.

## Acknowledgements

These ideas were shaped by discussions with Brendan Bradley, Alice Carter, Ron Dahl, Monique Ernst, Nathan Fox, Abby J. Fyer, Christian Grillon, Amanda Guyer, Donald F. Klein, Rachel G. Klein, Ellen Leibenluft, Shmuel Lissek, Karin Mogg, Chris Monk, Erin McClure, and Laurie Wakschlag.

The opinions and assertions contained in this paper are the private views of the authors and are not construed as official or as reflecting the views of the NIMH or the Department of Health and Human Services.

## Correspondence to

Daniel S. Pine, NIMH-Building 15-K, Room 110, MSC-2670, Bethesda, MD 20817-2670, USA; Email: daniel.pine@nih.gov

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Manuscript accepted 8 January 2007

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