13

Anxiety Disorders in Children and Adults: A Cognitive, Neurophysiological, and Genetic Characterization

Andrei C. Miu
Laura Visu-Petra

ADULT ANXIETY: CONCEPTUAL ISSUES RELEVANT TO THE CLINICIAN

Anxiety disorders are the most common category of mental disorders worldwide, placing a substantial burden on patients, their families, and society. The World Mental Health Survey Consortium reported 12-month prevalences of anxiety disorders that ranged from 2.4% in Shanghai, China, to 18.2% in the United States (Demyttenaere et al., 2004). The European Study of the Epidemiology of Mental Disorders has also investigated anxiety disorders' prevalence, risk factors, and burden and service use by mental patients in a sample of 213 million young and elderly adults from six European countries (i.e., Belgium, France, Germany, Italy, the Netherlands, and Spain). The data indicated that 12-month and lifetime prevalences of any anxiety disorder are 14.5% and 8.4% in the European population, respectively (Alonso & Lepine, 2007; see also Kessler, Chiu, Demler, Merikangas, & Walters, 2005).

Several factors contribute to the individual and social burden of anxiety disorders (Kessler, 2007). First, anxiety disorders are highly persistent; approximately 60%–70% of survey respondents with a lifetime anxiety disorder reported that their anxiety had been active within 6–12 months before the interview. Second, anxiety disorders are highly comorbid with other anxiety disorders and mood disorders. In addition, the lifetime prevalence of comorbid anxiety and depression has apparently increased in recent cohorts. Third, anxiety disorders are associated with substantial impairments in both productivity (e.g., work absenteeism, unemployment) and social roles (e.g., social isolation, marital disruption). Last but not least, anxiety disorders have an early age of onset (i.e., medians around 15 years) and they are associated with pervasive delays in seeking professional treatment.

The number of diagnostic categories for anxiety disorders has increased across the editions of the *Diagnostic and Statistical Manual of Mental Disorders*

(*DSM*). For instance, only 3 anxiety disorder categories existed in the *DSM-II* (American Psychiatric Association, 1968) as opposed to 12 categories in the *DSM-IV* (American Psychiatric Association, 1994). This increase in anxiety disorder categories has been viewed either as an effect of the greater precision in the classification of disorders, or, on the contrary, as evidence of the modest reliability of many diagnostic categories. Criticisms emphasize the increased empirical consideration of unique features of emotional disorders, made at the expense of shared or overlapping features that are equally relevant to prevention, etiology, and course of disorders (Andrews, 1996; Buckley, Michels, & Mackinnon, 2006). Although significant agreement on the presence of defining symptoms of *DSM* disorders has been empirically supported, considerable unreliability has in contrast been reported for categorical severity specifiers (i.e., mild/moderate/severe; Di Nardo, Moras, Barlow, Rapee, & Brown, 1993). This has led to the exclusion of severity specifiers for panic disorder (PD) and agoraphobia in *DSM-IV.* In addition, not only have some structured interviews (e.g., the lifetime version of the Anxiety Disorders Interview Schedule for *DSM-IV*; Di Nardo, Brown, & Barlow, 1994) been revised to make them consistent with *DSM-IV* criteria, but conceptual revisions have also been made to reflect the position that many features of emotional disorders operate on a continuum rather than in a categorical (i.e., presence/absence) mode. Therefore, these instruments can now inform diagnostic assessment of the key and associated features of a broad range of conditions, irrespective of whether a formal *DSM-IV* diagnosis is under consideration. Although assessments based on such structured interviews have acceptable to excellent reliability, the main difficulties arise when clinicians try to apply *DSM* categorical cutoffs to features rated on continuous dimensions (Brown, Di Nardo, Lehman, & Campbell, 2001). Disagreement on whether symptoms are sufficient in number, severity, or duration to meet *DSM-IV* diagnosis criteria is a common source of unreliability that suggests the necessity of revising the *DSM* by including dimensional rather than categorical criteria.

In addition to the limitations of the categorical approach to diagnostic assessment, the *DSM-IV* classification system has been confronted with a rapidly expanding body of literature identifying and linking genetic, neuroanatomical, neurophysiological, and cognitive differences in anxiety disorders. Multidisciplinary research in biological psychiatry and neuroimaging genetics has recently started to document so-called endophenotypes or intermediate phenotypes (Gottesman & Gould, 2003). Endophenotypes are subclasses of a diagnostic category, which are characterized by psychobiological markers that are more reliably associated with genetic variations (i.e., polymorphisms or mutations) than with the diagnosis category itself. For instance, endophenotypes of several anxiety disorders, characterized by preferential processing of threat (e.g., angry faces), increased amygdala activation, and reduced prefrontal control over amygdala activation to threat, as well as reduced response to selective serotonin (5-HT) reuptake inhibitors (SSRIs), have been associated with the short variant of a common polymorphism in the upstream regulatory region of the human 5-HT transporter gene (5-HTT; Canli & Lesch, 2007; see also Crisan et al., 2009). To date, research on endophenotypes of mental disease has amply demonstrated that the methodological and empirical advances in psychology, neuroscience, and interdisciplinary fields could and should influence the next generation of psychiatric diagnostic systems.

The *DSM-IV* is mostly based on cognitive and behavioral criteria, with the exception of a psychophysiological sign (i.e., exaggerated startle response) included in the diagnosis of post-traumatic stress disorder. Previous versions of the *DSM* included psychophysiological criteria (e.g., autonomic hyperarousal) for the diagnosis of other disorders such as generalized anxiety disorder (GAD). The reason for the their exclusion was related to their lack of reliability, but it has been acknowledged that elimination of these objective criteria has made the distinction of generalized anxiety disorder from mood disorders, for instance, problematic (Brown, Barlow, & Liebowitz, 1994). Today, a wide array of more reliable psychophysiological methods is available, and methodological standards (e.g., Blumenthal, Cuthbert, Filion, Hackley, Lipp, & Van Boxtel, 2005; Fridlund & Cacioppo, 1986; Jennings, Berg, Hutcheson, Obrist, Porges, & Turpin, 1981; Malik et al., 1996; Picton et al., 2000; Pivik, Broghton, Coppola, Davidson, Fox, & Nuwer, 1993) limit procedural idiosyncrasies. Many would agree that psychology and neuroscience have developed enormously in the past decades and it is time that these advances were systematically taken into account in psychiatric diagnosis.

However, endophenotype research has only recently started to develop, and some of the reported associations between genetic variations and psychobiological phenotypes cut across current diagnostic categories. For instance, 5-HTT polymorphisms have been associated with both anxiety and mood disorders. Whether this situation suggests a radical revision of current diagnostic categories or the still insufficient specificity of endophenotypes is difficult to say at present. In addition to this issue, the practical validity of including psychobio-

S___
E___
L___

logical diagnostic criteria that, however reliable, are still based on methods (e.g., functional neuroimaging) that are not widely available represents another apparent drawback in the systematic consideration of endophenotype research for diagnosis purposes. Nonetheless, the field is moving toward the investigation of interacting effects of multiple genetic polymorphisms on a still wider array of psychobiological measures, some of which (e.g., electroencephalogram-derived measures) are available and affordable (Miu, 2008). This warrants future improvements in the specificity of endophenotypes in relation to standard psychiatric diagnosis and the increasing influence of this research on psychiatric diagnosis systems.

The current diagnostic standards reflect the extensive research on pathogenetic cognitive factors that has been carried out in the last few decades. By employing experimental methods from cognitive and social psychology, psychophysiology, and more recently neuroscience, researchers have identified a host of cognitive and physiological differences thought to play critical roles in the etiology and pathogenesis of anxiety disorders. Under the influence of this type of research, theories of anxiety disorders have moved away from the stimulus-response models that dominated from the 1920s until the 1970s to information-processing models (H. J. Eysenck, 1976; Rachman, 1977). Behaviorist models viewed anxiety disorders as chronic attempts to avoid confrontation with fear-evoking cues or abnormal associations between stimuli and responses. For instance, phobia was described as an intense classically conditioned fear developed when an initially neutral stimulus (e.g., the white rat in the famous Little Albert case) was paired with a traumatic event (e.g., the frightening gong in the same case; Watson & Rayner, 1920). In line with learning theories (e.g., Wagner & Rescorla, 1972), conceptualizations of anxiety disorders acknowledged that the "signal value" of a stimulus as predictor of conditioning indicated the need for "informational models" and the refocalization of overly simplistic contiguity theories on the meaning of stimulus and response (Reiss, 1980).

The main assumption of cognitive models of anxiety disorders is that the emotional labeling of stimuli, particularly those that are perceived as aversive, plays a key role in the etiology, maintenance, and treatment of anxiety disorders (Eysenck, 1997; M. W. Eysenck, Derakshan, Santos, & Calvo, 2007; Mathews & Macleod, 1994, 2005; Williams, Mathews, & MacLeod, 1996). Cognitive research on anxiety has supported the view that anxiety disorders involve the dysregulation of otherwise adaptive emotions that have evolved to signal threat. Anxiety is a normal human emotion that can be characterized by increased autonomic activity; subjective feelings of tension; cognitions involving fear and worry; and sometimes even behaviors like verbal incoherence, avoidance of anxious stimuli, motor immobility, or tremor (Kowalski, 2000). Based on animal and human studies, some researchers have distinguished anxiety from fear based on cognitive appraisal, overt behaviors, and/or neurobiological underpinnings. Whereas fear would be the emotional response to an identifiable threat, relying on amygdala activity, and associated with active behavioral avoidance, anxiety would instead be the emotional response to an unidentifiable or anticipated threat, relying on septo-hippocampal activity, and associated with active exploration for risk assessment or active avoidance (Blanchard & Blanchard, 1990; Gray & McNaughton, 2000; Lazarus, 1982).

Notwithstanding this distinction between anxiety and fear, Foa and Kozak (1986) were among the first to emphasize that emotional disorders "involve excessive response elements (e.g., avoidance, physiological activity) and resistance to modification" as well as "impairments in mechanisms for the processing of fear-relevant information" (p. 21). In other words, emotional disorders are based on altered "fear structures" or programs to escape dangers, revealing what threat means and which responses are appropriate, including the physiological activity that prepares the individual for escape (Foa & Kozak, 1986). In similar functionalist accounts of emotions, other authors have also argued that anxiety is part of a defensive mechanism against potential dangers (Calvo, Avero, & Miguel-Tobal, 2003; Keltner & Gross, 1999). By biasing cognitive (e.g., attention, interpretation, memory, decision making) and physiological processes (e.g., autonomic modulation of the heart), anxiety facilitates anticipatory threat detection and mobilizes resources before an actual harm occurs.

These effects or biases of anxiety on cognition and physiology were first described in relation to anxious states, sometimes called stress (for a distinction between stress and anxiety, see Lazarus, 1993), in healthy individuals. The individual differences approach to anxiety, which was pioneered by Freud (1924) and Cattell and Scheier (1958), has led to the subsequent psychometric delimitation of trait anxiety (TA), that is, a generalized and enduring predisposition of certain individuals to develop states of anxiety (Endler & Kocovski, 2001; Spielberger, 1985). Extensive research has shown in the past decades that TA involves a greater probability of developing anxious states to mild or ambiguous stimuli and/or upregulations of the intensity or duration of these states. Why is TA be important for the clinician? The medical model, as exemplified by the *DSM,* is of a

categorical nature and identifies clinical or pathological developments of anxiety based on a number of criteria. Cognitive psychologists have instead approached individual differences in the type of anxiety (i.e., subclinical) that does not qualify for an anxiety disorder diagnosis. Their extensive work has documented the similarity of cognitive and physiological biases in TA and anxiety disorders and has accredited the view that TA and other affective traits are important risk factors for emotional disorders (Brandes & Bienvenu, 2006: Lonigan, Vasey, Phillips, & Hazen, 2004; Mathews & MacLeod, 2005). The genetic, neuroanatomical, and neurophysiological similarities between TA and anxiety disorders, identified in recent years, have further supported this position (see Miu, Miclea, & Houser, 2008). According to current theories and research, the distinction between subclinical and clinical anxiety is a matter of degree rather than quality. In light of the foreseeable transition from categorical to continuous diagnosis criteria for anxiety disorders, understanding the variation of cognitive and physiological biases along subclinical and clinical dimensions of anxiety is extremely important for both researchers and clinicians. Therefore, this chapter will review cognitive and physiological biases identified in nonclinical participants, as well as in anxiety disorders patients; in the second part of the chapter, a developmental perspective upon the same dimensions will be provided.

COGNITIVE BIASES IN ANXIETY DISORDERS IN ADULTS

Difficulties in differentiating depression and anxiety based solely on subjective or self-report measures were an important aspect of the context that gave rise to the popularity of cognitive theories and experimental methods of assessing cognitive processing in anxiety in the 1980s. The high comorbidity of mood and anxiety disorders and high correlations between self-report scales assessing depressive and anxious symptoms made the quantitative justification of diagnostic decision difficult and suggested that discriminating between anxiety and depression strictly on the basis of emotional phenomenology was doomed to be problematic (R. Beck & Perkins, 2001). Cognitive theorists argued that cognitive content was different in anxiety and depression, with thoughts concerning physical and psychological threat in anxiety, and negative assessments of the self, the world, and the future in depression (e.g., A. T. Beck, 1976). In addition, the temporal focus of these cognitions differed in that anxious thoughts were future oriented, whereas depressive thoughts were past oriented (Tellegen, 1985). In light of the inability of subjective measures to discriminate between anxiety and depression, it was also argued that more objective, experimental measures of cognitive processing could be used (Mathews & MacLeod, 1994). Once such measures were developed and refined, the search for cognitive biases in anxiety (tendencies to process information so as to favor certain types of emotional valence or meanings; Mathews & MacLeod, 2005) began to grow exponentially in mainstream psychology. These biases can characterize various stages of information processing by favoring the attentional selection of emotional over neutral stimuli; biasing the interpretation of ambiguous stimuli toward threatening meanings; increasing the availability of threat-related information in memory; and, last but not least, augmenting risk perception and risk taking in decision making.

Two main approaches to identifying cognitive biases in anxiety have been taken (Williams et al., 1996). The first investigated whether the tendency to selectively attend to emotional information facilitates performance on tasks that can benefit from the processing of such information. For instance, it was found that the visual and auditory thresholds to stimuli that are related to subjective concerns are indeed lower in patients with emotional disorders (e.g., Foa & McNally, 1986). The second approach has been to describe how the selective processing of emotional stimuli alters performance in tasks where this tendency would be disruptive. For instance, some of the most widely used assessments of this are the emotional Stroop, the attentional probe, the homophone interpretation, and the homograph relatedness judgment tasks.

In the emotional Stroop task, participants are presented with emotional and neutral words and they must rapidly name the color of the words while ignoring their meaning. This task was derived from the original color naming task described by Stroop in 1935, after it was observed that the latency of color naming increases under those circumstances that semantically prime the meaning of the words used in the task (e.g., self-referent words when the participant performs the task in front of a mirror; see Geller & Shaver, 1976). Thus the length of latency of naming the color of emotional words—an effect called emotional interference—provides an index of the tendency to selectively attend to emotional information in anxiety, which makes the task of ignoring the meaning of negatively valenced words particularly difficult in anxiety (Williams et al., 1996). In one of the first studies that tested this hypothesis, patients with clinical anxiety related to social or

S___
E___
L___

physical threat displayed increased latencies in naming the color of threatening words, and the magnitude of this effect was higher for physically threatening words (e.g., "disease," "cancer") in patients with physical anxiety than for those with social anxiety (Mathews & MacLeod, 1985). Similar findings were reported in spider phobics, who displayed delayed color naming on spider-related words, but no difference in the latencies on other emotional words compared to healthy control participants (Kindt & Brosschot, 1997; Watts, McKenna, Sharrock, & Trezise, 1986). Similar effects have been replicated in a wide range of anxiety conditions, with a grand mean latency difference of 48 ms between emotional and non-emotional words (Williams et al., 1996). However, one of the observations that emerged early from emotional Stroop research on anxiety indicated that performance of this task is disrupted particularly when the words are related to the central theme of patients' anxiety: rape-related words for rape victims (Foa, Feske, Murdock, Kozak, & McCarthy, 1991); social threat for patients with social phobia (Hope, Rapee, Heimberg, & Dombeck, 1990; Mogg, Bradley, Dixon, Fisher, Twelftree, & McWilliams, 2000); catastrophe themes and physical threat for PD patients (McNally, Riemann, Louro, Lukach, & Kim, 1992); and Vietnam trauma themes for Vietnam veterans with PTSD (McNally, Kaspi, Riemann, & Zeitlin, 1990).

Another issue that emerged from this kind of research is related to whether the emotional interference characterizes automatic or strategic modes of information processing. Automatic information processing is independent from attentional resources and insensitive to voluntary control, whereas strategic information processing denotes the involvement of both attentional mechanisms and voluntary control (McNally, 1995; Wells & Mathews, 1994). This issue has been related to the specificity of cognitive biases in anxiety and depression. According to mainstream theories, processing is biased toward selective processing of threat at automatic stages of information processing (e.g., detection and preattentional orientation) in anxiety, before that information has entered conscious awareness, whereas depression involves biased processing of emotionally negative information at strategic stages of information processing (e.g., elaboration of the meaning), after that information has entered conscious awareness (Mathews & MacLeod, 1986). Alternatively, anxiety is characterized by cognitive biases in attention (e.g., assessed with emotional Stroop tasks), and depression is characterized by biased memory (MacLeod, 1990; Mathews, 1990).

Several approaches have been developed to test the prediction of preattentional biases in the emotional Stroop task. First, a comparison between supraliminally and subliminally presented words was employed (Mogg, Bradley, Williams, & Mathews, 1993). In the subliminal condition, emotional and neutral words were presented for brief intervals (e.g., 1 ms), followed by the supraliminal presentation of meaningless strings of letters (i.e., mask) that remained on the screen until participants responded. The main finding was that the patients with GAD, but not those with major depression, displayed significant emotional interference effects in both the supraliminal and subliminal conditions. One of the implications of these results concerned the utility of cognitive therapy in reducing the unconscious cognitive biases toward the processing of threat in anxiety, an issue that has been theoretically and empirically addressed by cognitive therapists. Similar findings were reported in a study that investigated the effects of TA, state anxiety, and relevance of emotional words to the stressor (i.e., a proximal exam) on emotional Stroop performance (MacLeod & Rutherford, 1992). Elevated state anxiety increased emotional interference effects on all subliminal threatening words in high-TA participants, and it decreased these effects in low-TA participants. In addition, elevated state anxiety increased interference effects on emotional words unrelated to the exam, but it decreased emotional interference on exam-related words—these effects were independent of TA. These results were taken to indicate that elevated state anxiety increases the automatic tendency to selectively process threat in high-TA but not low-TA participants. The former are thus characterized by an "unstable feed forward system" that intensifies automatic cognitive biases under stress, whereas the latter "enjoy the benefits of a homeostatic emotional system" that will automatically screen out threatening information in order to reduce the level of state anxiety (MacLeod & Rutherford, 1992, p. 489). In the supraliminal condition, high-TA participants displayed a strategic tendency to avoid negatively valenced emotional information related to the source of state anxiety, an effect that they shared with low-TA participants. This indicated strategic control over cognitive biases in high-TA participants. The conclusion was that "both high TA normals under stress, and clinically anxious patients, may display an equivalent automatic pattern of processing selectivity, favoring threat related information, but that high TA normals alone, unlike clinical patients, may be able to reduce the emotional impact of this automatic bias by strategically imposing the opposite pattern of selectivity on the processing of stress relevant emotional information" (MacLeod & Rutherford, 1992, p. 490).

A different approach to the selectivity of attention in anxiety involved a "separated Stroop task" in which

distracter words and target patches of color were presented above one another, and participants were instructed to name the color of the patch and ignore anything else on the card (Fox, 1993). The words were both names of colors (i.e., non-emotional distracters) that were either congruent or incongruent with the color of the simultaneously presented patch and words differing in emotional tone, some of which were thus emotional distracters. The results indicated that high-TA participants displayed longer color-naming latencies both when the patches were presented with threatening emotional distracters and when the color name distracters were presented. It was concluded that this indicates the general difficulty that high-TA participants have ignoring distracting information, which raises the issue of the specificity of attentional biases to threat-related information rather than distracters in general. A similar conclusion was reached for GAD patients (Mathews, May, Mogg, & Eysenck, 1990). However, these studies have not disputed the preattentional bias toward the processing of threat, which has been replicated (e.g., MacLeod & Hagan, 1992; for negative results in clinical anxiety, see Buckley, Blanchard, & Hickling, 2002; Gotlib, Kasch, Traill, Joormann, Arnow, & Johnson, 2004). Indeed, in an emotional Stroop analog with images of faces—faces are viewed as more salient signals of social and emotional information than words—it has been shown that TA influenced emotional interference to masked, but not supraliminal fearful, faces, and it also predicted activation of the basolateral part of the amygdala during the processing of the former emotional stimuli (Etkin et al., 2004). Potential explanations for the occasional attentional bias in depression, but not anxiety, are related to comorbid anxiety in depressed patients, or the prolonged exposure conditions (e.g., Gotlib et al., 2004), which allows for the development of the strategic tendency of depressed participants to look longer at stimuli related to their sad mood, as well as for the early attention to threat in anxious patients to be superceded by later avoidance (Mathews & Macleod, 2005). The brief presentation of words eliminated the attentional bias toward negative words (e.g., "hopeless," "misery") that was found in conditions involving naturally occurring or laboratory-induced sad moods, and fairly long (e.g., > 500 ms) exposure of words (Bradley, Mogg, & Lee, 1997). In contrast, the masked presentation of words did not affect the attentional bias toward threatening words in anxiety, irrespective of the sad mood. Therefore, the duration of stimulus exposure and the comorbidity of anxiety and depression may explain some of the negative results in studies of emotional Stroop. It has also been suggested that methods such as the attentional probe task may be more sensitive than the emotional Stroop to the attentional bias that characterizes anxiety.

The attentional probe task involves the brief presentation of two words or pictures that differ in emotional tone, in symmetrical locations above and below a central fixation point. These stimuli are followed after some 500 ms by a small visual probe that appears in the location of either word. As soon as they detect the probe, participants are supposed to push the button that corresponds to the part of the screen in which the probe appeared (MacLeod, Mathews, & Tata, 1986). As a reflection of their tendency to allocate attention to the spatial location in which a threatening stimulus appeared, faster responses to probes presented in that location are expected in participants with anxiety. Both high-TA participants and patients with clinical anxiety display speeded detection of the probes that appear in the spatial location where threatening stimuli had appeared (Koster, Crombez, Van Damme, Verschuere, & de Houwer, 2004; Wilson & MacLeod, 2003). A series of experiments offered evidence that high TA is associated with faster detection of probes that occurred in the same location as masked threatening faces, but not happy faces (Mogg & Bradley, 1999). Moreover, the magnitude of this effect increased if the faces were subliminally presented in the left half of the screen, which probably restricted their processing to the right hemisphere. This observation is in line with the documented role of the right hemisphere in emotional surveillance and the anterior activation asymmetry theory of affective style (e.g., Davidson, 2002).

The attentional probe has been particularly useful in approaching the mechanisms supporting the selective allocation of visual attention toward the locus of threatening information. Individual differences in attentional bias have been explained in terms of the level of stimulus threat (i.e., "urgency threshold"; Mathews & MacLeod, 2005, p. 171) that marks the transition from active avoidance to active attention. In a study in which location was cued with neutral or angry faces, low levels of stimulus threat were associated with increased latencies to detecting the probe (avoidance), whereas high levels of stimulus threat were associated with faster detection (vigilance) of the probe (Wilson & MacLeod, 2003). In addition, the urgency threshold that marked the transition from avoidance to vigilance was lower in anxious than in non-anxious participants.

Another mechanism supporting the attentional bias in anxiety may be related to difficulty in disengaging from the threatening information, instead of selective

S___
E___
L___

attention drawn to the locus of the threatening stimuli (Fox, Russo, Bowles, & Dutton, 2001). In other words, does anxiety modulate how threat draws or holds attention? Two studies using modified attentional probe tasks approached this issue. The first study cued a single spatial location using threatening or non-threatening stimuli and hypothesized that the fastened detection of probes that appeared in the threat-cued location (i.e., so-called valid trials) would indicate facilitated engagement with threat, whereas slowed detection of probes that appeared opposite to threat-cued locations (i.e., invalid trials) would indicate facilitated disengagement from threat (Derryberry & Reed, 2002). Anxious participants were slower in probe detection on invalid threat-cued trials, but not faster than non-anxious participants in valid threat-cued trials. This seems to support the hypothesis of facilitated disengagement from threat in the attentional bias characteristic of anxiety. However, a follow-up study cued a spatial location using the gaze direction of a centrally presented fearful face. Both the faster detection of the probe in valid trials and its slowed detection in invalid trials were increased in anxious compared to non-anxious participants (Mathews, Fox, Yiend, & Calder, 2003). Therefore, effects of anxiety on neither the engagement nor disengagement from threat can be discarded. Disengagement difficulties may predominate when threatening stimuli are encountered incidentally (Mathews & MacLeod, 2005).

The homophone interpretation task investigates homophones having both threatening and non-threatening meanings (e.g., "guilt-gilt," "die-dye"), but a distinct spelling for each meaning (M. W. Eysenck, MacLeod, & Mathews, 1987). The underlying assumption is that anxiety biases the interpretation of homophones in favor of the threatening meaning. Comparing the percentage of spellings that corresponded to the more threatening of the two meanings of homophones, it was found that patients with GAD, even those who had been recovered for 6 months, chose the threatening meaning significantly more often than control participants (M. W. Eysenck et. al, 1987). Therefore, GAD patients tend to interpret ambiguous information in a threatening way. Another study used the same task to test whether state anxiety influences the degree to which contextual cues (e.g., the word "death" or "hair" presented on a screen as participants hear the homophone [dī]) influence the spelling of the word corresponding to the emotional or neutral meaning of homophones (Blanchette & Richards, 2003). The results indicated that state anxiety induced when participants are lead to believe that their performance is videotaped increased the probability that participants would choose to spell the homophone according to its emotional meaning when the emotional context (e.g., "death" in the example above) was presented. This effect was replicated even when the emotional context was presented subliminally, supporting the existence of an automatic bias of anxiety on interpretation of homophones.

In the homograph relatedness judgment task, homographs offering both threatening and non-threatening interpretations (e.g., "stroke," "conviction") are first presented on a screen. Some 500 ms later, a pair of words is displayed, only one of which is semantically associated with one of the meanings of the previously presented homograph. Participants have to choose the word in the pair that is related to the homograph that was previously presented, and it is expected that anxiety accelerates responses when the associate is related to the threatening meaning of the homograph (Wilson, MacLeod, Mathews, & Rutherford, 2006).

Both the homophone interpretation task and the homograph relatedness judgment task are measures of the online interpretations of ambiguous stimuli made at the time of their encounter. Other studies have used offline measures of interpretation biases concerning inferences on ambiguous stimuli presented at other times. For instance, one study used emotional and neutral short passages related to social or evaluative situations, followed by a questionnaire that required the interpretation of factual details presented in the target texts (Brendle & Wenzel, 2004). Particularly when the passages were self-relevant, socially anxious individuals made fewer positive and more negative interpretations of details in the texts. These offline measures have generally shown that anxiety is associated with biases toward negative interpretations of ambiguous stimuli (Mathews & MacLeod, 2005). For instance, patients with PD interpret descriptions of physical sensations as symptoms of catastrophic disease (Richards, Austin, & Alvarenga, 2001), whereas patients with social phobia predict disastrous outcomes for social situations (Stopa & Clark, 2000).

The evidence in favor of memory biases in anxiety disorders is mixed. In order to extend the predictions of automatic information-processing biases in anxiety and strategic-processing biases in depression, many studies have investigated both implicit and explicit memory. Implicit memory involves indirect tests (i.e., without specific instructions for participants to search their memory) of information that is learned as an unintended effect of previous experience. For instance, in a common test of implicit memory, participants are asked to complete a list of word stems with the first word that comes to mind, therefore without any specific referral

to the study list that was previously presented. Priming is an implicit memory effect that refers to the increased probability that the word stems will be completed with words that appeared in the study list. Explicit memory, on the other hand, refers to consciously controlled retrieval of previously learned information, and it is tested by free recall or recognition.

According to an early theory (Williams, Watts, MacLeod, & Mathews, 1988), anxiety disorders are characterized by orientation to threat during automatic stages of information processing, which is expected to increase priming of this information, and avoidance of further elaboration on threat in strategic stages of information processing, which is expected to decrease explicit retrieval of this information. This pattern of bias may contribute to pathogenesis of anxiety disorders by preventing habituation to threatening stimuli. This model was consistent with the finding of poorer memory for threatening than nonthreatening information (Mogg, Mathews, & Weinman, 1987). Actually, GAD patients recognized fewer threat words and more nonthreat words than controls in this study, which suggested that they actively avoid elaborative processing of threat and therefore have poorer recall of such information. Similar studies investigated implicit and explicit memory biases in relation to TA, and with the exception of three early studies (Nugent & Mineka, 1994; Reidy & Richards, 1997a, 1997b), they found no memory bias (Bradley, Mogg, & Williams, 1994; Brendle & Wenzel, 2004; Calvo et al., 2003; Dalgleish, 1994; Harrison & Turpin, 2003; Oldenburg, Lundh, & Kivistö, 2002; Reidy, 2004; Richards & French, 1991). Another study that compared GAD patients with healthy volunteers on tests of explicit and implicit memory (Mathews, Mogg, May, & Eysenck, 1989) found increased priming in the clinical group, but no differences in a cued-recall task. Due to its inclusion instruction (i.e., "Complete the stems with words presented in the study list *or* words that first come into mind"), cued recall is taken to rely on both automatic and controlled processes of memory (see Toth, Reingold, & Jacoby, 1994).

Although studies do not generally support explicit memory biases in GAD or social phobia, there is consistent evidence for explicit memory biases in PD, and some degree of support for explicit memory biases in PTSD and obsessive-compulsive disorder (OCD; for review, see Coles & Heimberg, 2002). Several studies indicated increased free recall and recognition of threatening passages and words in PD, in comparison to corresponding neutral and positive stimuli (Nunn, Stevenson, & Whalan, 1984; Cloitre & Liebowitz, 1991). This is consistent with clinical observations of the tendency of PD patients to report vivid memories of previous threatening experiences and sensations. Fewer studies have investigated implicit memory in PD, and the positive findings of memory biases have been limited to certain experimental conditions (e.g., low noise), and they have not been replicated (see Coles & Heimberg, 2002). Better success has been reported in studies of explicit memory in PTSD, a disorder that involves intrusive and repetitive reexperiences of the trauma. Vietnam veterans with PTSD recalled more threatening than nonthreatening words (Vrana, Roodman, & Beckham, 1995), and in comparison to controls, adult survivors of childhood sexual abuse with PTSD recalled fewer of the positive and neutral words that they were instructed to remember (McNally, Metzger, Lasko, Clancy, & Pitman, 1998). Moreover, PTSD patients also displayed increased false recall of words associated with those in the study list, which may suggest their increased susceptibility to false memories (Zoellner, Foa, Brigidi, & Przeworski, 2000). Similarly, theories of OCD have implicated memory deficits since the beginning of the 20th century by explaining checking rituals based on impaired retrospective memory. Indeed, OCD patients recalled more negative words, which they had been instructed to forget in a directed forgetting task, than controls (Wilhelm, McNally, Baer, & Florin, 1996). However, as concluded by Coles and Heimberg (2002), the evidence for memory biases in PTSD and OCD is sparse and far from definitive.

One of the issues that the authors of this review have identified as crucial to the development of this field is related to the nature of the encoding tasks. Procedures that encourage the shallow processing of the study material are unlikely to find evidence for explicit memory biases. Using a task in which emotional "oddballs" appeared in lists of neutral words, one of our studies found that TA did not affect the recall of threatening "oddballs" but did influence the recall of adjacent neutral stimuli (Miu, Heilman, Opre, & Miclea, 2005). Therefore, although the recall of threatening stimuli did not differ, it retroactively interfered with the ongoing encoding of the immediately preceding neutral stimuli in high-TA participants. This increased "emotion-induced retrograde amnesia" associated with TA was found in free but not cued recall, and it was not influenced by the depth of processing. The emotion-induced retrograde amnesia has been replicated in anxiety-prone participants with a common functional polymorphism in the regulatory region of 5-HTT gene (Strange, Kroes, Roiser, Tan, & Dolan, 2008).

Recent research has increased the focus on decision-making biases in anxiety, and it has been argued that these biases play a crucial pathogenetic role in

S___
E___
L___

anxiety disorders (Ernst & Paulus, 2005; Miu et al., 2008; Paulus, 2007). Decision making is a key component of human cognition and behavior, involving the ability to choose between possible outcomes associated with uncertain benefits and penalties (van Leijenhorst, Crone, & Bunge, 2006). One of the best-documented effects of anxiety on decision making involves risk perception and risk avoidance. An early study used a risk evaluation task in which participants were supposed to evaluate the probability and personal utility of events described in several passages (Stober, 1997). High TA was associated with increased probabilities and negative utilities (i.e., costs) when the events were negative, and decreased probabilities and utilities (i.e., benefits) when the events were positive. These results suggest that anxiety is associated with a pessimistic bias in the perception of risk and chance. Similar findings have been reported for acute stress disorder, a condition that most often develops into persistent PTSD (Harvey & Bryant, 1998). Compared with trauma-exposed controls without acute stress disorder, acute stress disorder patients overestimated the probability of somatic and social harm, as well as the adverse effects of such negative external events (Smith & Bryant, 2000). Both high-TA individuals and patients with anxiety disorders also report or display decreased risk taking in subjective or behavioral measures of this bias. In one well-known experimental risk-taking task (i.e., balloon analog risk task), participants can earn financial rewards by pumping balloons presented on a screen—different balloons have variable explosion points, and once a balloon explodes, the money deposited for pumping that balloon is lost. Anxiety is associated with reduced mean pumps per unexploded balloon, which indicates risk aversion (Maner et al., 2007). In addition, anxious individuals have an increased susceptibility to a decision-making error known as the framing bias, which is induced when two otherwise equivalent alternatives are phrased differently (e.g., participants have to decide whether to keep or gamble a sum of money within "gain frames" announcing that "provided an initial sum of 50 dollars, you gain 20 dollars," and "loss frames" described as "provided an initial sum of 50 dollars, you loose 30 dollars"). Kahneman and Tversky (1984) found that framing biases decision making by inducing risk avoidance in the gain frames, and risk taking in the loss frame. Recent studies have indicated that these biases are increased in anxiety, which indicates decreased rationality in this type of decision making (Lauriola & Levin, 2001). Increased intolerance for uncertainty is another characteristic of decision making in anxiety, which has also been implicated in the pathogenesis of GAD (Krain et al., 2008). Intolerance for uncertainty correlated with amygdala and prefrontal activation in a sample of GAD adolescents, which would explain why anxiety biases the assessment and formation of preferences among possible options (Ernst & Paulus, 2005; Krain et al., 2008).

Anxiety has been associated with hyperarousal or increased interoception (i.e., homeostatic sensing of the internal state of the body), as well as increased top-down modulation of interoceptive signals through biased attention and interpretation. Accordingly, anxious individuals may show "an altered pattern of aversive somatic markers during the assessment stage of decision making . . . , as well as during the experience of outcome" (Ernst & Paulus, 2005, p. 602). We recently used an Iowa gambling task and psychophysiological correlates of emotional response to find this exact pattern in participants selected for extreme TA (Miu, Heilman, & Houser, 2008). The Iowa gambling task (IGT) simulates real-life decision making in the way it factors uncertainty of premises and outcomes, as well as reward and punishment (Bechara, Damasio, Damasio, & Anderson, 1994). It measures the degree to which individuals learn to choose small immediate gains associated in the long term with smaller losses over large immediate gains associated in the long term with yet larger losses. High TA was associated with a pattern of increased anticipatory skin conductance prior to advantageous trials, increased heart-rate deceleration to punishment, and impaired decision making. These results clearly indicate that high TA is associated with defective modulation of somatic signals, coupled with disrupted discrimination of advantageous and disadvantageous choices in decision-making tasks involving learning from emotional cues. The new field of neuroeconomics promotes multidisciplinary approaches to decision-making biases, and therefore further progress in the investigation of anxiety-related biases in risk perception, risk taking, intolerance to uncertainty, assessment of alternatives, and evaluation and experience of outcomes is warranted (Miu et al., 2008; Paulus, 2007; see also Rahman, Sahakian, Cardinal, Rogers, & Robbins, 2001).

After this brief review of evidence of cognitive biases in anxiety disorders, the reader is now prepared to have a critical, empirically driven perspective on cognitive models of anxiety disorders. Remember that these models and the experimental approaches to assessing cognitive biases have grown in popularity in light of the difficulties in differentiating anxiety and depression based on self-report measures. An important issue that has been broached by cognitive models of anxiety is

___S
___E
___L

related to the stage of information processing in which biases that are specific to anxiety act. Perhaps the best-known theory addressing this issue is that of A.T. Beck and Clark (1997), which incorporates previous experimental and theoretical work (A.T. Beck, Emery, & Greenberg, 1985; Mathews & MacLeod, 1994; McNally, 1995). According to this theory, the erroneous or biased interpretation of stimuli as threatening, as well as the individual's underestimation of coping resources and rescue possibilities in the environment, is a core feature of anxiety disorders. Clinical anxiety is viewed as an exaggerated perception of danger that differs only in degree from subclinical anxiety. This theory also acknowledges that anxiety involves a pattern of cognitive, behavioral, subjective, and physiological changes that arise from a three-stage information-processing sequence.

The first stage, or the orienting mode, involves the use of automatic processing to detect stimuli and assign an initial processing priority through the allocation of attentional resources. The recognition of emotional valence (i.e., positive or pleasant, negative or unpleasant, and neutral) and personal relevance are the typical outputs of this stage of processing. Anxiety disorders are characterized by a biased orienting mode, which involves preferential processing of negatively valenced, personally relevant stimuli.

The second stage, called immediate preparation, relies on the activation of a primal mode defined as a cluster of schemata. Such a schema is the threat mode, a pattern of cognitive, behavioral, and physiological responses that seeks to minimize danger and maximize safety. The threat mode involves autonomic arousal, behavioral mobilization and inhibition, and constriction of cognitive processing onto the threatening stimulus, as well as the production of repetitive and automatic thoughts and images involving threat and danger, and feelings of fear. This stage of processing relies on a combination of automatic and strategic processes that create a conscious impression of threat. This impression is based on processing that may occur outside awareness. However, the primary threat appraisal or semantic analysis of the stimulus begins at this stage. Processing at this stage is rigid and dichotomous and associated with intolerance to uncertainty and ambiguity. It results in preferential processing of negatively valenced information at the expense of positively valenced stimuli, and activation of negative automatic thoughts with themes of threat and danger.

The third stage of processing, secondary elaboration, involves a metacognitive mode and rests on strategic processes. Individuals reflect on their anxious thoughts, feelings, and sensations, which were activated in the primal mode. A type of contextualized processing takes over and consequently schemata representing the current concerns and personal issues of the individual become activated. This stage of information processing implements a secondary appraisal process in which individuals evaluate the availability and effectiveness of their coping resources in relation to the perceived threat. It can result in the escalation or decline of anxiety, as well as in a subsidence of anxiety due to escape or avoidance behaviors prompted by the primal mode. Worry and the search for safety signals are characteristic of this stage of strategic elaboration on perceived threat.

Considering that information-processing biases arise in automatic stages of information processing, it has been argued that cognitive, verbally mediated therapy would be ineffective in influencing them. While acknowledging that verbal mediation is a necessary but not sufficient component of any anxiety therapy, A.T. Beck and Clark (1997) have nonetheless argued that teaching patients a strategy that maximizes elaboration and reflection on their threat-related cognitions can be beneficial. Indeed, a study that compared Beck's cognitive-behavioral therapy (CBT) and behavior therapy (i.e., learning to control symptoms through relaxation, reducing avoidance of threatening stimuli through graded exposure, building confidence through reengagement in pleasurable and rewarding activities) indicated that the former type of therapy is more effective than the latter in GAD, with improvements in most of the measures of anxiety, depression, and cognitions that were taken (Butler, Fennell, Robson, & Gelder, 1991). Other studies have shown that cognitive-behavioral therapy in the test-retest interval reduces interference of masked threat words in emotional Stroop tasks, and the degree of this reduction correlates with reductions of anxious thoughts that persist at follow-up (Mathews, Mogg, Kentish, & Eysenck, 1995; Mogg, Bradley, Millar, & White, 1995; but see also Devineni, Blanchard, Hickling, & Buckley, 2004). Even treatment with SSRIs reduces interpretive biases in a homophone interpretation task, and this effect on cognitive biases correlates with reductions of self-reported anxiety (Mogg, Baldwin, Brodrick, & Bradley, 2004). Therefore cognitive biases reflect relief from anxiety symptoms.

The direct test of the hypothesis that cognitive biases play a causal role in anxiety disorders has come from studies that manipulated cognitive biases and measured their impact on psychopathology. These studies have only recently begun, but their results are already promising. For instance, a four-session training

S___
E___
L___

to interpret descriptions of ambiguous events in an increasingly positive manner reduced TA (Mathews, Ridgeway, Cook, & Yiend, 2007). Using parallel versions of the attentional probe task, in which probes always appear in the location of the threat or neutral word, another important study indicated that the training with these probes led to faster or slower detection of the probes that replaced threat or nonthreat words, respectively. Moreover, the latter bias predicted lower increases in negative mood in a subsequent stressful anagram task (MacLeod, Rutherford, Campbell, Ebsworthy, & Holker, 2002). Similar trainings designed to induce attentional avoidance of threat in high-TA students predicted decreased state anxiety in response to an impending examination (Mathews & MacLeod, 2002; MacLeod, 2008). The reduction of interpretive biases of ambiguous passages also induced decreased anxiety reactivity to a stressful video (Wilson et al., 2006). These data provide strong support for causal contributions of cognitive biases to anxiety. The extension of these studies to clinical anxiety is warranted. Testing the impact of cognitive bias reduction on a wider array of anxiety symptoms (e.g., subjective, behavioral, and physiological) will consolidate the clinical potential of these experimental interventions. Indeed, it may turn out that "cognitive processing bias may be the common pathway underlying reductions in vulnerability to emotional disorders, whether due to medication, cognitive training, or conventional psychological treatment" (Mathews & MacLeod, 2005, p. 187).

However, investigations of the biased automatic processing of negatively valenced stimuli (i.e., the valence hypothesis) and specificity of themes in self-reported automatic thoughts of anxiety patients (i.e., the cognitive content hypothesis) have been challenged. An emotional Stroop task with masked and unmasked presentation of the stimuli has been used to investigate the two hypotheses in PTSD and PD (Buckley et al., 2002). The results indicated no bias in color naming of threat words in the masked version of the emotional Stroop task. PTSD but not PD patients only showed interference effects on negatively valenced stimuli in the unmasked versions of the task. In contrast, the cognitive content hypothesis was supported in this study, with PD patients showing increased interference effects on unmasked disorder-specific threatening stimuli. Other studies have challenged even the cognitive content hypothesis. A meta-analysis of 13 studies indicated that depression and anxious cognitive content share most of their variance, with an average correlation across studies of .66 (R. Beck & Perkins, 2001).

Whereas the empirical support for the important contribution of cognitive biases to anxiety disorders is extensive and sound, the studies that reported negative findings suggest that these contributions may differ between anxiety disorders. In addition, they also highlight the possibility that anxiety disorders arise from interactions among different representational systems (Dalgleish, 2004). Specific cognitive models emphasizing the role of catastrophic misinterpretation of bodily sensations and panic self-efficacy in PD (Casey, Oei, & Newcombe, 2004; D. M. Clark, 1986), increased self-directed attention triggered by social situations, and decreased attention to positive external cues in social anxiety have thus been developed for each of the anxiety disorders (for review, see Mathews & MacLeod, 2005). These models explain why these patients anticipate negative reactions from others and fail to effectively encode actual social feedback (Alden & Taylor, 2004; D. M. Clark & Wells, 1995; Rapee & Heimberg, 1997), disorganized memory representation induced by extreme emotions experienced at the time of trauma, in interaction with premorbid intelligence in PTSD (Brewin & Holmes, 2003; Buckley, Blanchard, & Neill, 2000; Dalgleish, 2004), and negative beliefs about worry or metacognitive "worry about worry" in GAD (Borkovec & Roemer, 1995). However, even in regard to these specific models, it has been argued that the incorporation of research on the impact of early learning histories, temperamental vulnerabilities, personality risk markers, and inefficient emotion regulation strategies is long overdue (Amstadter, 2008; Brandes & Bienvenu, 2006; Gross, 1998, 2002; Mineka & Zimbarg, 2006). The consideration of these factors has started to inform strategies for prevention of anxiety disorders (Bienvenu & Ginsburg, 2007; Feldner, Zvolensky, Babson, Leen-Feldner, & Schmidt, 2008; Feldner, Zvolensky, & Schmidt, 2004).

GENETIC AND PHYSIOLOGICAL MARKERS IN ADULT ANXIETY DISORDERS

The recent empirical and methodological integration of human genetics and neuroscience has started to result in major advances in our understanding of the biology of human mental health and disease (Hariri & Lewis, 2006). A wide array of methods and approaches has been applied in multidisciplinary investigations of anxiety disorders, including twin and adoption studies, genetic linkage and genetic association studies, and electrophysiological and functional neuroimaging studies.

The genetic contributions to a trait or disease have been investigated in three main types of research

designs pertaining to behavioral and molecular genetics. First, twin and adoption studies compare monozygotic and dizygotic twins raised together and apart to determine what part of the variance of a trait or disease can be attributed to additive and non-additive genetic effects, as well as shared (family-wide) and non-shared (individual-specific) parts of the environment (Plomin, DeFries, McClearn, & McGuffin, 2008). For instance, a twin study indicated moderate (31%) genetic effects, minimal shared environmental effects (15%), and substantial non-shared environmental effects (54%) for TA (Lau, Eley, & Stevenson, 2006). Therefore, most of the variance in TA is accounted for by genetic influences (e.g., polymorphisms in the 5-HTT gene) and family-wide factors such as dysfunctional early parent-child relationships, neighborhood conditions, and the socioeconomic status of the parents (Carlson & Sroufe, 1995; Caspi, Taylor, Moffitt, & Plomin, 2000; Miech, Caspi, Moffit, Wright, & Silva, 1999). Studies comparing the prevalence of panic among relatives of PD probands and the relatives of controls have consistently indicated high familial loading of this disorder. For instance, a meta-analysis of 13 such studies found that the lifetime prevalence of panic was 10.7% among the relatives of PD probands, compared to 1.4% among the relatives of healthy controls—this gives a relative risk of 6.8 for PD (Gorwood, Feingold, & Ades, 1999). Indeed, twin studies of PD estimated heritability of PD to be as high as 44%, which places this disorder at the top of heritable anxiety disorders (Kendler, Walters, Neale, Kessler, Heath, & Eaves, 1995). Family and twin studies of specific phobia have reported that the relative risk for phobia is 3.1, and the estimated heritability is 35% (Fyer, Mannuzza, Chapman, Martin, & Kleon, 1995; Kendler, Neale, Kessler, Heath, & Eaves, 1992a). There are few such studies on the other anxiety disorders, and the results have been rather inconsistent (for review, see Merikangas & Pine, 2002).

AuQ1

The other two approaches to determining the genetic influence on a certain trait or disease are genetic linkage and genetic association studies. The former first determines if a specific DNA sequence from a certain chromosome is related to a trait or disease and then involves sequencing the genes in that portion of the chromosome in order to identify the variations (e.g., functional mutations or polymorphisms) that modify the functions of those genes in a manner that significantly influences the trait or disease under study. Genetic polymorphisms occur in >1% of a population, and they are thus more likely than less frequent mutations to influence the variance of a trait or disease in that population. For instance, the linkages of PD to mutations in adrenergic receptor or gamma-aminobutyric acid receptor A loci have been investigated, and the results were negative (Schmidt, Zoega, & Crowe, 1993; Wang, Crowe, & Noyes, 1992). Even genomic surveys that used 600 markers with known chromosomal locations (i.e., they serve as probes for the chromosomal location of the DNA sequence of interest) found no genetic linkage in PD. This lack of success in genetic linkage of anxiety disorders is probably related to factors such as their etiologic and phenotypic heterogeneity, the lack of reliable diagnostic thresholds, and their comorbidity with other forms of psychopathology (Merikangas & Pine, 2008). On the other hand, genetic association studies have identified several genetic polymorphisms that influence the behavioral and neurophysiological phenotype of anxiety. In these studies, the variants of genes that are known to influence a trait or disease are identified, and the frequency of alleles in samples with or without that trait is determined.

S___
E___
L___

A growing body of literature has investigated the influence of certain polymorphisms on various phenotypic aspects that are relevant to disease. One of the goals of these studies has been to focus on functional polymorphisms of the genes related to the neurotransmitter system that is targeted by the standard medication for a disease (e.g., SSRIs). Consequently, many genetic association studies have investigated genetic polymorphisms in the genes encoding the synthesizing and catabolizing enzymes, pre- and postsynaptic receptors, and molecules controlling intracellular trafficking and extracellular transport of 5-HT. For instance, 5-HTT is the initial molecular target of SSRIs that have antidepressant and anxiolytic functions. Its gene (SLC6A4) is located on chromosome 17q11-12 and encodes a transmembrane protein involved in the reuptake of 5-HT in the presynaptic neuron following its exocytosis to the synaptic cleft (Lesch, Wolozin, Murphy, & Reiderer, 1993; Ramamoorthy et al., 1993). We know of two polymorphic regions of 5-HTT: a 44-bp insertion/deletion polymorphism (5-HTTLPR, where LPR stands for "linked polymorphic region") in the promoter region of the gene, and a variable number of tandem repeats in the second intron of the gene (VNTR-in2; Hranilovic et al., 2004; Lesch et al., 1996). 5-HTTLPR alleles are commonly composed of either 14 or 16 repeated elements (Heils et al., 1996). The latter, called a long (L) allele, is more than twice as active as the former, called a short (S) allele, in terms of 5-HTT expression and uptake of 5-HT by platelets (Lesch et al., 1996). Lesch et al.'s landmark study also reported that 5-HTTLPR accounts for 7%–9% of the heritable variance of individual differences in anxiety, with the S homozygotes

displaying increased TA. Further studies have shown that S homozygotes display better therapeutic response to SSRIs, hyperactivation of the amygdala during the processing of threatening stimuli (e.g., fearful faces), and reduced volume of the gray matter in the anterior cingulate cortex and amygdala (Hariri et al., 2002; Heinz et al., 2007; Pezawas et al., 2005). Studies on the influence of 5-HTTLPR on autonomic responses have offered inconclusive results to date (Schmidt, Storey, Greenberg, Santiago, Li, & Murphy, 2000).

Recent research has identified a single nucleotide polymorphism within the L allele of 5-HTTLPR itself, and the observation that one of the alleles (L_G) is low functioning in comparison to the L_A allele (Hu et al., 2006) has led to more reliable findings in regard to the response to SSRIs among individuals with social anxiety (Stein, Seedat, & Gelernter, 2006). It has been suggested that the effects of low-functioning alleles of 5-HTTLPR develop particularly in individuals who are systematically exposed to stressors (Gunthert, Conner, Armeli, Tennen, Covault, & Kranzler, 2007). Almost a quarter of the individuals who have a stressful job and report symptoms of anxiety or depression are carriers of the S allele of 5-HTTLPR (Caspi et al., 2003). Indeed, the risk of GAD is almost double for individuals who have stressful jobs (Melchior, Caspi, Milne, Danese, Poulton, & Moffitt, 2007), of whom those carrying a low-functioning allele of 5-HTTLPR may be the most exposed. In addition, the VNTR-in 2 polymorphism in 5-HTT gene has been shown to contribute to anxiety disorders (e.g., OCD) and other psychiatric conditions with a major stress component (Ogilvie et al., 1996; Wendland et al., 2008). The alleles of this polymorphism contain 9, 10 (i.e., S alleles), or 12 (i.e., L alleles) copies of 16- or 17-bp repeats in the second intron of the 5-HTT gene. It is likely that additional sources of variation in this and other genes (e.g., tryptophan hydroxylase, 5-HT receptors 1A and 2A) will be uncovered, and these may also prove to influence the 5-HT regulation of the stress response and its contribution to anxiety disorders. In light of the estimated 100 such polymorphisms that contribute to the variance of complex traits and polygenic diseases, the current focus is on studying epistatic interactions between these and other genetic polymorphisms (Brown & Hariri, 2006; Canli & Lesch, 2007; also see Table 13.1). The great potential of these studies comes in part from the wide diversity of measures by which the anxious phenotype can be related to genetic polymorphisms.

Electrophysiological measures have been extensively used to characterize the phenotype associated with anxiety disorders. These measures index autonomic and central nervous system correlates of emotional responses. It has long been held that exaggerated fear responses are common to all anxiety disorders. With the success of animal models in documenting the involvement of the amygdala and adjacent structures in fear (see Davis, 1998; LeDoux, 2000), one of the most extensively used psychophysiological measures has been the fear-potentiated startle. There are at least two reasons for the popularity of this measure: it relies on the activation of the amygdala, and it can be measured in both animals and humans. The human startle reflex is a series of unconditioned motor responses (i.e., forward thrusting of the head, a descending flexor wave reaction extending through the trunk and knees) to an intense and unexpected stimulus (Landis & Hunt, 1939). In humans, a brief (e.g., 40 ms) and loud (i.e., 90–115 dBA) burst of white noise (i.e., the startle probe) is presented, and the eye blink, the most consistent component of the startle pattern (Grillon, 2002), is recorded in order to measure the latency and magnitude of the startle reflex. The fear-potentiated startle refers to the increased latency and magnitude of the startle reflex during aversive states, such as those elicited by the anticipation of an electric shock. Whereas the startle reflex relies on a simple reflex arc (i.e., cochlear root neurons, neurons in the nucleus reticularis pontis caudalis, and motoneurons in the spinal cord), the fear-potentiated startle relies on an additional projection from the central nucleus of the amygdala to the nucleus reticularis pontis caudalis (Grillon, 2002). In light of the demonstration that negatively valenced stimuli (e.g., affective pictures) presented before the startle probe potentiates startle response (Lang, Bradley, & Cuthbert, 1990), the potentiation of the startle reflex has been used as an objective index of the perceived aversiveness of a stimulus and the cognitive bias toward threat. Pictures of spiders for spider phobics (de Jong, Visser, & Meckelback, 1996), anticipation of public speaking for individuals with social anxiety (Cornwell, Johnson, Berardi, & Grillon, 2005), emotional imagery for individuals with PD (Cuthbert, Drobes, Patrick, & Lang, 1994), and verbal threat or administration of the probes in a dark environment for PTSD patients (Grillon, Morgan, Davis, & Southwick, 1998a, 1998b) have been shown to potentiate the startle reflex. Therefore, elevated fear-potentiated startle seems to support the hyperactivity of the amygdala in anxiety disorders (see Cuthbert, Lang, Strauss, Drobes, Patrick, & Bradley, 2003; Grillon, 2002; Lang, 1995).

Psychophysiological measures of autonomic functions have also been useful in describing anxiety disorders. They have been used to test the assumption

13.1 Functional Genetic Polymorphisms That Influence Dimensions of Emotion (Other Than 5-HTTLPR)

GENE	LOCATION	PROTEIN AND FUNCTION	POLYMORPHISM(S)	RELEVANT EFFECTS	REFS.*
TPH-1	Chromosome 11	Tryptophan hydroxylase 1 (TPH1); hydroxylation of l-tryptophan to 5-hydroxytryptophan	SNPs: A-779C (*U*, upper allele) and A-779C (*L*, lower allele)	*U* carriers show higher scores of anger-related traits	(Nielsen, Dean, & Goldman, 1992; Rujescu et al., 2002)
TPH-2	Chromosome 12	Tryptophan hydroxylase 2 (TPH2): same as TPH1, but specific to the brain	SNPs: G-703T (rs4570625)	*T* variant correlates with trait anxiety; it influences amygdala reactivity; its frequency is higher in patients with personality disorders	(Brown et al., 2005; Canli, Congdon, Gutknecht, Constable, & Lesch, 2005; Gutknecht et al., 2007; Herrmann et al., 2007)
5-HT1A	Chromosome 5	5-HT1A receptor: autoreceptor on presynaptic soma, and postsynaptic receptor for 5-HT	27 known SNPs: e.g., C-1019G (rs6295); C-1018G; Ile-28Val (rs1799921); Arg-219Leu (rs1800044); Gly-22Ser (rs1799920); Pro-16Leu; Gly272asp	C-1019G: carriers of the *G* allele have higher scores of anxiety and neuroticism	(Strobel et al., 2003; Zetzsche et al., 2008)
5-HT2A	Chromosome 13	5-HT2A receptor: G-protein coupled postsynaptic receptor for 5-HT	SNPs: G-1438A (rs6311); T-102C (rs6313); His-452Tyr (rs6314)	*C* homozygotes display more anger and aggression-related behaviors; negative correlation with trait anxiety	(Giegling, Hartmann, Moller, & Rujescu, 2006; Rybakowski et al., 2006)
MAO-A	Chromosome X	Monoamine oxidase A (MAO-A): primary catabolizing enzyme for synaptic 5-HT, noradrenalin, and dopamine	VNTR in the upstream promoter region: 3.5 or 4 repeat elements (high-expressing MAOA-H variant) vs. 3 or 5 repeats (low-expressing MAOA-L variant)	Male carriers of the low expressing variant show dysregulated amygdala activation and increased functional coupling with ventromedial prefrontal cortex	(Buckholtz et al., 2008; Gross & Hen, 2004)

COMT	Chromosome 22	Catechol-O-methyl-transferase (COMT): postsynaptic catabolizing enzyme for catecholamines (i.e., dopamine, adrenalin, noradrenalin)	SNP: Val-158Met (rs4680)	Val/Val genotype is associated with 3-4 times higher COMT activity compared to Met/Met; the former genotype is associated with higher amygdala and prefrontal activation to emotional faces in panic disorder patients	(Baekken, Skorpen, Stordal, Zwart, & Hagen, 2008; Domschke et al., 2008; Lotta et al., 1995; Wray et al., 2008)
BDNF	Chromosome 11	Brain-derived neurotrophic factor (BDNF): neurotrophic factor that contributes to neural development and plasticity	SNP: Val66Met	- Met/Met is associated with lower neuroticism	(Hunnerkopf, Strobel, Gutknecht, Brocke, & Lesch, 2007)

Notes: The references are only illustrative. SNP = single nucleotide polymorphism; VNTR = variable-number tandem repeat.

of tonic or phasic hyperarousal in anxiety. Heart-rate variability (HRV) is a non-invasive electrocardiographic index of the autonomic control of the heart, which has been studied extensively in anxiety disorders (Cohen, Matar, Kaplan, & Kotler, 1999; Friedman & Thayer, 1998; Friedman, Thayer, Borkovec, Tyrrell, Johnson, & Columbo, 1993; Gorman & Sloan, 2000). HRV reflects oscillations in the interval between consecutive heartbeats, and it results from the dynamic or homeostatic interaction of sympathetic and parasympathetic (vagal) inputs to the sinoatrial node (Braun, Kowallik, Freking, Hadeler, Kniffki, & Meesmann, 1998; Robinson, Epstein, Beiser, & Braunwald, 1966). To date, the relationships between sympathetic and vagal influences on the heart are not completely understood (Eckberg, 1997). However, a reduction in the parasympathetic innervation is considered to leave the heart exposed to unopposed stimulation by the sympathetic nervous system, and consequently vulnerable to ventricular arrhythmia and sudden death (Gorman & Sloan, 2000). The analysis in the frequency domain involves the distribution of oscillations in at least two frequency bands and the determination of power in each of these bands. Power in the high-frequency band (˜0.15–0.4 Hz in adults) has been associated with respiratory sinus arrhythmia and is considered to reflect vagal modulation of the heart, whereas power in the low-frequency band (˜0.05–0.15 Hz) probably reflects a complex interplay between sympathetic and vagal influences (Eckberg, 1997; Kingwell, Thompson, Kaye, McPherson, Jennings, & Esler, 1994; Malik et al., 1996). Reduced HRV in anxiety and affective disorders is empirically supported. For instance, several studies have reported that HRV is reduced in patients with panic disorder (Klein, Cnaani, Harel, Braun, & Ben-Haim, 1995; Sullivan, Kent, Kleber, Martinez, Yeragani, & Gorman, 2004; Yeragani et al., 1991) and even the children of patients with panic disorder (Srinivasan, Ashok, Vaz, & Yeragani, 2002). Patients who reported frequent severe panic attacks showed reduced HRV in a variety of laboratory conditions (e.g., quiet rest, shock avoidance, face immersion, isoproterenol infusions) and a dominant sympathetic control of heart rate associated with reduced vagal tone (Friedman et al., 1993; Yeragani, Pohl, Srinivasan, Balon, Ramesh, & Berchou, 1995). High TA is also associated with reduced HRV, decreased vagal tone, and higher vagal withdrawal during mental stress (Bleil, Gianaros, Jennings, Flory, & Manuck, 2008; Miu, Heilman, & Miclea, 2008). Also, low HRV predicts exaggerated startle responses to threat of shock in both healthy participants selected for TA and PD patients (Melzig, Weike, Hamm, & Thayer, 2008).

Various other psychophysiological indices have shown their utility in distinguishing between anxiety disorders. For instance, GAD and PD patients may report similar levels of anxiety symptoms under stressful conditions (i.e., a mental arithmetic task and images of severe panic attacks), but the latter, or at least a subgroup, can be distinguished by lower levels of end-tidal CO_2 at baseline, which seem to suggest a chronic state of relative hypocapnia (Hegel & Ferguson, 1997). On the other hand, GAD patients seem to be more sensitive to changes in physiological arousal, since it was shown that they can detect significantly more of changes in skin conductance fluctuations (i.e., resulting from the sympathetic stimulation of sweat gland secretion) during a signal detection task (Andor, Gerlach, & Rist, 2008). In comparison to PD, PTSD patients display decreased parasympathetic regulation of the heart (i.e., respiratory sinus arrhythmia) and increased sympathetic activity (i.e., skin conductance amplitude) at baseline, but blunted electrodermal responses under threat-of-shock conditions (Blechert, Michael, Grossman, Lajtman, & Wilhelm, 2007). Indeed, a recent meta-analysis indicated increased resting heart rate, which may reflect reduced parasympathetic control over the heart and slow skin conductance habituation to startling probes, as well as larger facial muscle and heart-rate responses to idiographic trauma cues (Pole, 2007; see also Lindauer, van Meijel, Jalink, Olff, Carlier, & Gersons, 2006).

Psychophysiological recordings during exposure to stressful conditions have also provided interesting insight into phobia. Blood pressure increases more in anxiety and anger than in happy states, and it has been suggested that these emotional effects may be facilitated in individuals with more labile blood pressure (James, Yee, Harshfield, Blank, & Pickering, 1986). The case study of a patient with PD with agoraphobia indicated that systolic blood pressure during exposure to the anxiogenic situation (i.e., traveling on a chairlift) strongly (and positively) correlates with stress (Lewis & Drewett, 2006). Other studies show that high TA is associated with increased heart rate during preparation of a to-be-evaluated speech, and the same is true for social phobia (Gonzalez-Bono, Moya-Albiol, Salvador, Carrillo, Ricarte, & Gomez-Amor, 2002; Hofmann, Newman, Ehlers, & Roth, 1995; but see Mauss, Wilhelm, & Gross, 2003).

Electroencephalography (EEG) recordings and functional neuroimaging have been used extensively to study central neurophysiological markers of anxiety disorders. The frontal lateralization of EEG power in the alpha band (i.e., 8–13 Hz) has been related to emotional valence, motivation, and affective style (Davidson, 2003; Harmon-Jones, 2003; Heller, 1993). Decreases in EEG alpha power suggest increases of cortical activity induced by the thalamic suppression of alpha waves (Larson et al.,

S___
E___
L___

1998). Greater right-to-left frontal EEG alpha power reflects processing of positive valence and approach-related motivational tendencies, whereas greater right-to-left frontal EEG alpha power reflects processing of negative valence and withdrawal-related motivational tendencies. There is much controversy regarding the degree to which the frontal asymmetry of EEG alpha power reflects emotional valence (the valence-arousal hypothesis) or motivational direction (the approach-withdrawal hypothesis). However, the correlation of the right resting frontal EEG alpha power and a negative affective style characterized by reduced emotional resilience is extensively supported. For instance, people with high TA (Petruzzello & Landers, 1994), social phobia (Davidson, Marshall, Tomarken, & Henriques, 2000), and PD (Wiedemann, Pauli, Dengler, Lutzenberger, Birbaumer, & Buchkremer, 1999) and even children whose parents have social phobia (Campbell, Schmidt, Santesso, Van Ameringen, Mancini, & Oakman, 2007) show increased right-lateralized frontal EEG alpha power, and a recent meta-analysis confirmed moderate effects of anxiety on this EEG index (Thibodeau, Jorgensen, & Kim, 2006). Benzodiazepines reverse the pattern of frontal activity in monkeys, and the degree to which the greater relative right frontal activation changes into greater relative left frontal activation correlates with reductions in behavioral signs of anxiety (Davidson, Kalin, & Shelton, 1992). An optical neuroimaging study confirmed the relationship between anxiety and frontal activation asymmetry. During a state of anticipatory anxiety, the levels of oxyhemoglobin, which indicates a local rise in energy demands, increased more in the right than in the left medial prefrontal cortex. This increase was positively correlated with individual differences in anxiety (Morinaga et al., 2007).

Following Heller's suggestion (Heller, Nitschke, Nitschke, Etienne, & Miller, 1997; but see Mathersul, Williams, Hopkinson, & Kemp, 2008) that subtypes of anxiety are associated with different patterns of cerebral activation asymmetry (i.e., anxious arousal is associated with greater right posterior activation whereas anxious apprehension is associated with greater left anterior activation), it has been reported that arousal symptoms correlate with right-sided parietal activation in PTSD female Vietnam War nurse veterans (Metzger et al., 2004). Other EEG-derived measures have also been applied in studies of anxiety disorders. For instance, frontal midline theta activity, which has been shown to reflect feelings of relief from anxiety during mental tasks, correlates with reductions in anxiety symptoms in GAD (Suetsugi et al., 2000).

Given the fact that TA is substantially genetic in nature, one would expect it to be associated with differences in brain structure and function. Indeed, an early magnetic resonance spectroscopy study indicated that TA is associated with higher concentrations of the excitatory neurotransmitter precursor N-acetylaspartate in the orbitofrontal cortex (Grachev & Apkarian, 2000). Subsequent neuroimaging work supported the view that TA is associated with structural and functional differences in the neural structures related to emotion and emotion regulation, particularly in the temporal and frontal lobe. For instance, a recent magnetic resonance imaging (MRI) study showed that both women and men with high TA displayed reduced volume of the right hippocampus; however, only the women also had reduced volume of the left anterior prefrontal cortex (Yamasue et al., 2008). TA has also been negatively correlated with resting regional cerebral blood flow in the left parahippocampal gyrus and orbitoinsular junction, as well as other regions in the frontal, temporal, and parietal cortex (Sugiura et al., 2000). Finally, functional MRI studies have indicated that activity in frontal and medial temporal lobe structures also varies as a function of TA in cognitive tasks. TA was correlated with anterior cingulate response to emotionally positive stimuli (Canli, Amin, Haas, Omura, & Constable, 2004; for discussion, see Hamann & Harenski, 2004). Also, TA predicted activation of the basolateral amygdala to subliminally processed fearful faces (Etkin et al., 2004; see also Mujica-Parodi et al., 2009).

Amygdala hyperactivity during symptom provocation or negative emotional processing has been supported by functional neuroimaging studies in individuals with PTSD, social anxiety, specific phobia, OCD, and PD. A recent meta-analysis that included functional neuroimaging studies in individuals with PTSD, social anxiety, and specific phobia analyzed the shared and specific neural activity in these conditions and tested whether data across studies support the view that limbic dysregulation is associated with prefrontal dysfunctions (Etkin & Wager, 2007). In various emotional processing conditions (e.g., emotional Stroop, reading of emotional passages, viewing of emotional pictures or emotional videos), patients with all three anxiety disorders displayed amygdala hyperactivity. The ventromedial prefrontal cortex, rostral anterior cingulate cortex, and thalamus were hypoactivated in PTSD and the activation of the former also correlated negatively with symptom severity in PTSD, but not social anxiety or phobia. Compared with PTSD, the hyperactivation of the amygdala was more specific to phobia, whereas the hyperactivation of the insula was common to phobia and social anxiety. This meta-analysis also found evidence of consistent correlation between ventromedial prefrontal cortex hypoactivity and amygdala and insula

hyperactivity. It was concluded that all three disorders involve exaggerated activation of the amygdala, but in addition, PTSD also involves dysfunctions of the neural circuits associated with emotion regulation (see Etkin, Egner, Peraza, Kandel, & Hirsch, 2006; Goldin, McRae, Ramel, & Gross, 2008). Although functional neuroimaging studies on clinical populations are limited by typical small sample sizes, heterogeneity in task design (e.g., block, single trial, or event-related designs), and patient characteristics (e.g., inherent comorbidity), meta-analyses allow us to determine the reliability of effects. This way, the identification of neural markers may help describe the mechanisms that are shared and specific to anxiety disorders, which will likely affect diagnosis, nosology, and development of new therapies in the future.

CHILDHOOD ANXIETY: EARLY VULNERABILITY MARKERS

Developmental studies have contributed to a life span perspective on the psychopathology of anxiety disorders. These disorders have typically been shown to begin early in life (Gregory, Caspi, Moffitt, Koenen, Eley, & Poulton, 2007; Kessler, Berglund, Demler, Jin, & Walters, 2005; Pine, Cohen, & Gurley, Brook, & Ma, 1998). Current approaches to pediatric anxiety (e.g., Pine, 2007; Vasey & Dadds, 2001) combine information from genetics, affective neuroscience, and clinical work, generating an information-processing framework to characterize cognitive functioning in this disorder. Such an approach attempts to reveal the mechanisms through which an early vulnerability status, combined with specific environmental experiences, can modify the neural circuitry underlying fear-related behaviors throughout development.

This section attempts to provide a state-of-the-art overview of current findings regarding early vulnerability signs for development of anxiety disorders in the clinical but also in the nonclinical at-risk population. The main findings suggest the fluidity of anxiety disorders throughout the life span, underscoring the need for a developmental perspective. A second premise is that vulnerability markers at different levels (genetic, neurological, behavioral) are connected to families of disorders rather than to a specific outcome (Pine, 2007). The following multilevel analysis of the vulnerability factors identified during childhood and adolescence will complement the preceding section on adult risk factors with the dynamics of anxiety disorders throughout development. The overall aim is to assist the clinician (viewed as a scientist-practitioner) in identifying early (often cumulative) risk factors for development of anxiety disorders, and to inform developmentally tuned prevention and intervention programs.

EPIDEMIOLOGY AND DIAGNOSTIC FEATURES

The early manifestations of anxiety disorders partially overlap with a typical pattern of fear development during childhood and adolescence. This normative ontogenetic parade (Scarr & Salapatek, 1970) consists of separation anxiety (6–22 months); stranger anxiety (6–24 months); fear of unfamiliar peers (20–29 months); fears of animals, darkness, and imaginary entities (2–6 years); performance anxiety (6–12 years); fear of physical harm and injury (8–16 years); and social anxiety (12–18 years; Egger & Angold, 2006; Pennington, 2002). An exaggeration of such typical concerns in terms of intensity or persistence beyond these age intervals indicates a potential anxiety disorder. Thus, there is a parallel ontogenetic scenario in the onset of specific subtypes of clinical anxiety: separation anxiety and specific phobias in middle childhood (ages 7–9), overanxious disorder in late childhood (10–13 years), social phobia in middle adolescence (15–16 years), and panic attacks in late adolescence (17–18 years), as reviewed by Merikangas and Pine (2002).

The classification of childhood anxiety disorders mimics the adult symptoms clustering in *DSM-IV* (American Psychiatric Association, 1994) and the tenth edition of the *International Classification of Diseases* (World Health Organization, 1992). According to *DSM IV*, separation anxiety disorder (SAD) is the only condition that is specifically classified as a "disorder first diagnosed in infancy, childhood or adolescence." An overview of diagnostic criteria and prevalence information for childhood anxiety disorders is beyond the scope of this chapter, but we refer the reader to comprehensive reviews by Cartwright-Hatton, McNicol, and Doubleday (2006); Schniering, Hudson, and Rapee (2000); Weems and Stickle (2005); and Vallance and Garralda (2008). Egger and Angold (2006) present an overview of the scarce research regarding preschool anxiety disorders and their assessment and treatment.

Under the general label of "childhood anxiety disorders" we refer to the *DSM-IV* nosological categories of SAD, panic disorder, selective mutism, OCD, GAD, social phobia, specific phobias, and PTSD. However, most of the developmental research has been conducted using diagnostic criteria from the *DSM-III* (American

Psychiatric Association, 1980), which has been shown to be relatively consistent (Kendall & Warman, 1996) with the newer categories in the *DSM-IV* (one essential change in the latter is the requirement of evidence of impairment for an anxiety disorder to be diagnosed). Therefore, at certain points in this chapter, we will refer to categories from the previous version of the *DSM,* such as overanxious disorder (consistent with GAD from *DSM-IV*) and avoidant disorder (relatively consistent with the newer social phobia in the *DSM-IV;* Kendall & Warman, 1996).

An important issue in delineating these clinical categories is their discriminant validity, namely, the degree to which they can be differentiated from each other and from other disorders of childhood. We believe that anxiety in children and adolescents is best conceptualized as falling along a clinical continuum (see the description of typical fears above), with accentuated intensity and persistence of symptoms as well as increasing life distress as a marker for the diagnosis of anxiety disorders. For some anxiety disorders (e.g., overanxious disorder, overanxious disorder), it has been difficult to disentangle clinical from nonclinical controls in terms of anxiety-provoking situations, distress, or subjective level of cognitive competence (Beidel, Silverman, & Hammond-Laurence, 1996). The introduction of the new category of GAD in the *DSM-IV* has revealed a better discriminative power, considering the larger number of worries in clinically anxious children (Tracey, Chorpita, Douban, & Barlow, 1997). However, at this first level of delineating clinical from nonclinical variations populations, the existing screening and diagnosis tools ensure a reasonably consistent differentiation (see Schniering et al., 2000). In terms of the prevalence of overall anxiety disorders, most studies have only targeted children over 6 years of age (and mostly over 11), with very heterogeneous results. The comprehensive review by Cartwright-Hatton et al. (2006) suggests a prevalence ranging from 3% (Ford, Goodman, & Meltzer, 2003) to 24% (Kroes et al., 2001) of children. This does not mean that the nonclinical population cannot be further investigated in terms of vulnerability to anxiety disorders. Vallance and Garralda (2008) suggest that more than 25% of non-referred children report subclinical symptoms and over 20% have subclinical phobias.

Looking at the level of individual anxiety categories differentiation, we see that a more complicated picture emerges, especially when we consider the developmental version of anxiety disorders. A high degree of overlap characterizes subtypes of anxiety disorders (Kessler et al., 1994). In clinical child and adolescent samples, over 50% of children with one primary anxiety diagnostic also met the criteria for an additional anxiety disorder (Alessi & Magen, 1988; Strauss & Last, 1993). In community samples, comorbidity rates are much lower (Lewinsohn, Zinbarg, Seeley, Lewinsohn, & Sack, 1997; Valleni-Basile, Garrison, Jackson, Waller, McKeown, Addy, & Cuffe, 1994). Using *DSM-III* criteria, research has revealed limited evidence for the distinctiveness of overanxious disorder (but more substantial evidence for the newer GAD; Tracey et al., 1997) and more consistent results for social phobia, simple phobias, and SAD (Last et al., 1987; Strauss & Last, 1993). Insufficient attention has so far been paid to OCD and to PTSD (Schniering et al., 2000). If we look at prevalence rates of individual anxiety disorders in this age group, again results are controversial (see Cartwright-Hatton et al., 2006, for a review), with SAD as the dominant primary diagnosis (about 4%), and different—but generally lower—rates for OCD, GAD, and social anxiety, and somehow higher rates for simple phobias.

A final discriminant validity analysis targets the distinction between childhood anxiety disorders and other psychiatric constructs such as depression. Some theoretical accounts (e.g., Clark & Watson, 1991; King, Ollendick, & Gullone, 1991) have argued that the overlap in brain mechanisms and the high comorbidity rates among the two suggest that we are dealing with a common underlying factor (negative affect) and with other factors specific to each of the two (physiological arousal vs. anhedonia). Or, as Pennington (2002) frames it, "someone with an anxiety disorder has a lower threshold for an acute stress response, which then remits, while someone with a depressive disorder is stuck in a chronic stress response" (p. 126), both responses also presenting an adaptive value if adequately adapted to real-life circumstances (Nesse, 1999). Early in development, anxiety disorders are more common than depressive disorders (Cartwright-Hatton et al., 2006), leading some researchers to suggest the idea of a developmental continuum, where anxiety precedes depression (Kovacs, Gatsonis, Paulaskas, & Richards, 1989; Selligman & Ollendick, 1998). In studies with children and adolescents, comorbidity rates between anxiety and depression have been found to range from 16% to 62% (Brady & Kendall, 1992). This high comorbidity rate is partially intrinsic to the overlapping diagnostic criteria (irritability, restlessness, fatigue, concentration difficulties) but may also be a result of the masked manifestations of the disorders during early development, which leads to confusion and misdiagnosis.

Perhaps as a reflection of this last point, other differential diagnoses have been considered to be between childhood anxiety disorders (considered "internalizing")

and behavior disorders ("externalizing"; Achenbach, 1985). Even if apparently opposite, these two types of disorders share some common features: interpretation of ambiguous information as threatening (Barrett, Rapee, Dadds, & Ryan, 1996; but see the difference at the level of response to threat) and diagnostic symptoms (restlessness, difficulties concentrating).

However, the value of a developmental approach does not reside in the recording of such static "snapshots" of manifestations and prevalence of anxiety disorders at different ages, but rather in a more realistic, dynamic view of their unfolding. At this point, some fundamental notions of a developmental psychopathology model (Cicchetti & Rogosh, 1996) have to be introduced, as they will also inform our multilevel analysis of vulnerability to anxiety. The notion of "equifinality" refers to the fact that similar outcomes can be reached from different initial states and through different pathways; "multifinality" reflects the fact that particular risk factors do not necessarily lead to the same outcome. A salient notion for anxiety research has been the idea of heterotypic continuity, or the notion that throughout development, the manifest form of psychopathology (and, most probably, the underlying circuitry as well) presents itself in various forms and leads to distinct outcomes. From this point of view, although pure etiological perspectives upon anxiety disorders are essential, they are not sufficient (Weems & Stickle, 2005), because different mechanisms can lead to distinct manifestations of anxiety disorders in children and adolescents, even if the initial risk factors are found to be similar.

Bearing this dynamic framework in mind, we can analyze the developmental stability and continuity of different childhood anxiety disorders. Two ideas that arose as a result of research in the field should be mentioned: anxiety disorders are extremely fluid across the life span, and early manifestations (or at-risk status in general) constrain but do not determine adult outcome, "raising questions about mechanisms that lead an underlying diathesis to be manifest or remain silent" (Pine, 2007, p. 632). Arguments for the second idea, concerning the lack of absolute deterministic power in the case of early anxiety disorders, result from studies revealing that a minority of at-risk individuals turn out to manifest adult disorders. Behavioral inhibition (Kagan, 1994) in toddlers predicts two- to fourfold increased risk for pediatric anxiety disorders (especially social phobia), but in terms of absolute risk, Pérez-Edgar and Fox (2005) show that no more than 50% of inhibited children develop pediatric anxiety disorders. In addition, about 50% of adolescents with anxiety disorder will develop adult psychopathology (Pine et al., 1998). The highest remission rates are for separation anxiety disorder, and the lowest for panic disorder (less than 75%), as discussed by Vallance and Garralda (2008).

We will not present the results of longitudinal studies including treatment interventions here (but see below). However, they suggest that most children completely recovered, although a significant portion (about one-third) still received a different diagnosis at the 3-year follow-up (Cantwell & Baker, 1987). In other studies, whereas the diagnosis of 15% of children had shifted to a different anxiety disorder at the 3- to 4-year follow-up, the diagnosis of 13% changed to a depressive disorder, and 7% to an externalizing disorder, which supports the idea of fluidity of anxiety disorders across the life span (Last, Perrin, Hersen, & Kazdin, 1996).

Children with social phobia, SAD, or GAD show a two- to threefold greater risk for adult anxiety disorders (Pine et al., 1998; Gregory et al., 2007). Concerning outcome specificity, data generally provide stronger support for social phobia and SAD than for GAD. A study investigating the stability of anxiety diagnosis during a 6-month interval revealed that many of the initial diagnoses changed but actually were most likely to change to another anxiety disorder or to shift to subclinical levels of anxiety disorders, still revealing a greater vulnerability toward developing an anxiety disorder (Beidel, Flink, & Turner, 1996). On the other hand, an 8-year follow-up of adolescents age 9–18 provides evidence for the stability of the subtypes of anxiety disorders, especially in the case of social and simple phobias, but less so in the case of overanxious disorder (Cantwell & Baker, 1989). The lack of agreement regarding outcome specificity in these studies also diminishes the validity of delineating separate childhood anxiety disorders.

Regarding the predictive value of early anxiety disorders for the development of other types of psychopathology and general psychiatric problems, there is evidence for nonspecific outcomes derived from behavioral inhibition. It appears that toddlers high in behavioral inhibition face a greater risk for major depressive disorder (Caspi, Moffitt, Newman, & Silva, 1996); similarly, pediatric GAD also predicts risk for both adult anxiety and major depression (Pine et al., 1998; Gregory et al., 2007). Anxiety disorders in childhood lead to a two- to fivefold increase in anxiety disorders, depression, suicide attempts, and psychiatric admissions later in life and is associated with increased rates of substance abuse (Vallance & Garralda, 2008).

A final source of evidence for the developmental continuity of anxiety disorders is represented by family studies, which will be reviewed next. The general conclusion is that anxiety runs in families, presenting strong

S___
E___
L___

cross-generational associations. In such cases, however, the developmental relationships might conceal the effects of genes, environment, and gene-environment interactions as possible causal mechanisms.

ETIOLOGY: GENETIC SUSCEPTIBILITY TO PEDIATRIC ANXIETY

In the pursuit of the etiological pathway to defining anxiety disorders, one essential question concerns the degree to which developmental continuities reflect the influence of genes or environment throughout the life span. While research on the genetics of anxiety in humans has primarily focused on adults (see above), in the late 1980s a series of studies appeared that made use of family and twin designs to investigate psychopathology earlier in development. An underlying aim was to find developmental shifts in genetic influences, which turned out to be a relatively common finding (e.g., Feigon, Waldman, Levy, & Hay, 2001; Topolski et al., 1997), with increasing age resulting in an increase in heritability (with a peak in early adolescence).

Comprehensive reviews of research into the genetics of childhood anxiety have been proposed (Eley, 1999; Gregory & Eley, 2007; Merikangas & Pine, 2002). Without aiming at a complete overview of this research, we have selected the main findings to help guide the clinician through recent findings regarding the genetic liability in the early development of anxiety disorders. From the beginning, it should be clear, however, that "to date, there remain no pathognomonic markers with which a presumptive diagnosis of an anxiety disorder may be made" (Merikangas & Pine, 2002, p. 867). The causes for such agnosticism include the difficulties of disentangling genetic from environmental contributions and their dynamic interplay throughout development, as well as the fact that many genes of small effect appear to be involved, rather than unique genetic causes. We will proceed with the review of main findings regarding familiality, heritability, gene locations, and environmental influences on childhood anxiety and sketch out some future directions (endophenotypes, at-risk populations, comorbidity) that might help elucidate the remaining mysteries in the field.

Familiality

Most studies have replicated the familial aggregation of all subtypes of anxiety disorders, with a three- to fivefold increased risk in the first-degree relatives of diagnosed probands (Merikangas & Pine, 2002). Moreover, this relationship appears to be bidirectional, so that children's anxiety also increases the risk for such a disorder in their parents (Beidel & Turner, 1997). Childhood onset of anxiety disorder (before the age of 20) is also associated with a greater familial risk for anxiety symptoms in relatives (Goldstein, Wickramaratne, Horwath, & Weissman, 1997), probably due to a higher concentration of familial risk factors in the proband (Pennington, 2002). Unfortunately, this type of study is not sufficient for delineating genetic and environmental influences on the development of anxiety disorders.

Heritability

Adoption studies rarely focus on childhood anxiety, so they won't be presented at this point. Twin studies attempt to disentangle gene-environment influences by comparing data from monozygotic (MZ) and dizygotic (DZ) twins. They estimate the extent to which interindividual variation in anxiety symptoms is influenced by additive genetics (A; heritability), common or shared environmental influences (C), and non-shared environmental (E) influences. The results reveal a heritability rate between 30% and 40% (Kendler et al., 1992b, 1993), with distinct values for particular anxiety disorders, although the influence appears to be general and less disorder specific. The results in child samples reveal a 59% heritability rate for maternal reports of manifest anxiety (Thapar & McGuffin, 1995).

In terms of individual anxiety disorders, results from a large sample of child and adolescent twins (Topolski et al., 1997) suggest different heritability for overanxious disorder (37%, with non-significant C) and SAD (non-significantly heritable, but with a moderately significant $c^2 = 40$). A different result was obtained by Feigon et al. (2001), who evaluated SAD symptoms in the 3–18 years age band and found evidence for both genetic and shared environmental effects, with genetic effects increasing and C effects decreasing with age. The results of Eaves et al. (1997) bring nuance to the findings in terms of sex differences: while heritability for SAD was insignificant for boys, it was high for girls. Finally, Bolton et al. (2006) found high heritability for SAD (73%), with the remaining variance attributable to non-shared environment.

Heritability estimates for specific phobias are usually high (about 65%; Lichtenstein & Annas, 2000; about 80% and the remaining variance attributable to E in Bolton et al., 2006; a wider range of 16%–55%, depending on the type of phobia, in Lichtenstein & Annas, 1997). This suggests that fears and phobias in young children are more attributable to genetic than to environmental

influences. In the case of GAD (or previously overanxious disorder), results suggest additive genetic effects of about 37% (Topolski et al., 1997), or 32% among female twin pairs (Kendler et al., 1992a). Panic disorder also appears to be subject to genetic liability (Skre, Onstad, Torgersen, Lygren, & Kringlen, 1993; Kendler et al., 1995). Few controlled twin studies have targeted OCD, and there is weak evidence for heritability in the case of this disorder (Carey & Gottesman, 1981; Hudziak, Copeland, Stanger, & Wadsworth, 2004; Lenane, Swedo, Leonard, Pauls, Sceery, & Rapoport, 1990).

Some of the factors responsible for the inconsistencies in results are the manner in which questionnaires are completed (via mail or through direct interviewing; Pennington, 2002); the respondent (parental reports generally produce higher genetic estimates than children's self-reports; Eaves et al., 1997), the evaluation of anxiety as a personality trait, as a collection of symptoms, or as a clinical disorder (see Gregory & Eley, 2007, for an overview of differences); and the focus on state or TA (results in a youth sample of 10–18 years pointed to genetic and non-shared E influences on TA, and shared and non-shared environmental influences on state anxiety; Legrand, McGue, & Iacono, 2000).

Pennington (2002) reviews data that reveal a striking genetic correlation (essentially 1.0) between symptom measures of anxiety and depression (using child self-reports), suggesting a complete genetic overlap on these two measures. Eley and Stevenson (1999) pursued and refined the same comparison, deriving less correlated factors between anxiety and depression as outcome variables, but again, the genetic correlation was very high (the shared genetic factor accounted for 80% of the phenotypic correlation). The hypothesis put forward by Pennington (2002) for the clinical differentiation of these two disorders is the existence of non-shared environmental influences (e.g., loss for depression).

Molecular Genetics

Heritability studies generate hypotheses identifying specific candidate genes that may function as vulnerability markers for anxiety disorders. As reviewed above, most genetic association studies have focused on serotonin and dopamine genes. The few developmental studies conducted so far have shown mixed findings in children regarding 5-HTT, emphasizing the association either between the possession of two copies of the short 5-HTT allele and shyness in the third and fourth grades (Battaglia et al., 2005) or between the long version of the 5-HTT allele and shyness (Arbelle, Benjamin, Golin, Kremer, Belmaker, & Ebstein, 2003), or revealing no association between this gene and anxiety/depression (Young, Smolen, Stallings, Corley, & Hewitt, 2003). For dopamine, there was evidence for a combined effect of the 7-repeat DRD4 allele and two copies of the short form in the promoter region of the serotonin transporter in infants' responses to anxiety-provoking situations (Lakatos et al., 2003). The functional polymorphism located in the promoter region of the 5-HTT gene has also been shown to moderate the effects of negative life events on depression symptoms in adolescents (Eley, Sugden, Gregory, Sterne, Plomin, & Craig, 2004).

Environment

In parallel with the need to specify candidate genes responsible for the heritability effects in the case of anxiety disorders, there is clearly a need to clarify the shared and non-shared environmental contributions to their development. One of the most relevant findings (and relatively unique compared to other disorders) supports the influence of shared environment on the development of anxiety disorders in children and adolescents. Shared family experiences during childhood thus appear to have a greater effect during childhood, an effect that diminishes in the later stages of life (Eley, 2001).

Environmental factors responsible for the early emergence of anxiety disorders might include acute and chronic stressors (e.g., maternal psychopathology; Armsden, McCauley, Greenberg, Burke, & Mitchell, 1990), modeling and some child-rearing practices (Krohne & Hock, 1991). Among the acute stressors, perinatal complications and prenatal exposure to substance use were not directly linked to the development of anxiety disorders, but rather to the development of behavior disorders (Allen, Lewinsohn, & Seeley, 1998; Merikangas, Avenevoli, Dierker, & Grillon, 1999). Stressful life events during adolescence were found to be predictive for both depressive and GAD symptoms (but only in females) in one of the few existing prospective studies (Pine et al., 2000). Exposure to early adverse experiences (separation or abuse) has been developmentally linked to posttraumatic stress disorder (Pynoos, Steinberg, & Piacentini, 1999).

However, in both clinical and community samples, the perception of environmental stress appears essential in mediating the stress-outcome relationship (Bernstein, Garfinkel, & Hoberman, 1989; Kashani & Orvaschel, 1990). Perceived lack of control (regarding access to food, water, and treats) induced in a quasi experiment

S___
E___
L___

with young rhesus monkey led to an increase in fear and reduced exploratory behavior (Mineka, Gunnar, & Champoux, 1986).

Among the child-specific non-shared environmental influences, friendships and low school achievement appear to be related to anxiety (Goodyer, Wright, & Altham, 1989).

Future Directions

One relevant direction for future research to pursue is prospective investigations into very early anxiety manifestations in children at genetic risk of developing anxiety disorders. This information would provide an evaluation of premorbid risk factors and signal early markers of diagnostic value for this disorder. Merikangas and Pine (2002) review the existing studies revealing specificity of parent-child concordance within broad categories of anxiety disorders, as well as a lack of specificity with respect to depression. The next section will review some of the typical characteristics of early anxiety manifestation.

Another fruitful line of research suggested by Gregory and Eley (2007) is the investigation of comorbidity in twin studies in order to compare cross-twin cross-trait correlations in MZ and DZ twins. This would help elucidate the common or distinct genes that influence two possible outcomes (e.g., anxiety and depression) in such pairs. One example of such a study (Eley, Bolton, O'Connor, Perrin, Smith, & Plomin, 2003) conducted with 4-year-old twins found modest associations between five types of anxiety symptoms (general distress, separation anxiety, fears, obsessive-compulsive behaviors, and shyness). An important extension of these studies would be inspection of successive comorbidity, with different disorders occurring at different points of the ontogenetic trajectory (e.g., Gregory, Eley, & Plomin, 2004; Silberg & Bulik, 2005; Silberg, Rutter, Neale, & Eaves, 2001).

Finally, as suggested previously by research with adult participants, it might be more relevant to focus on identifying endophenotypes, which are more proximal to genes activity and related to neurophysiological, biochemical, endocrinological, cognitive, or neuroanatomical characteristics of functioning in children with anxiety disorders (Gregory & Eley, 2007). The following section will attempt to reveal potential markers of such endophenotypes at multiple levels, which, in turn, might represent stronger criteria for identifying and treating anxiety disorders than current symptoms classifications.

OTHER INTRINSIC VULNERABILITY MARKERS

At this point in our analysis we will briefly present the intrinsic factors (ranging from the broad level of temperamental or personality predispositions to very specific psychophysiological and neurochemical responses) that have been shown to represent early signs of vulnerability to the development of anxiety disorders. Table 13.2 provides a synopsis of these markers, following the classification offered by Merikangas and Pine (2002). As the neural circuitry underlying threat-related behaviors can be considered an integral part of an information-processing approach, brain markers of childhood anxiety will be reviewed at greater detail in the next section.

First, a general predisposition toward anxiety disorders can be seen in specific temperamental or personality features such as behavioral inhibition, generally negative affectivity (although this is also a nonspecific predictor of psychopathology in general), low effortful control. We refer the reader to comprehensive reviews regarding temperament-anxiety relations by Clark (2005), Lonigan and Phillips (2001), Muris and Ollendick (2005), Ţincaş, Benga, and Fox (2006). However, the exact nature of this relationship is not clear, since temperament could play (1) a causal role, representing a predisposition to anxiety (especially amplifying the echo of a relevant stressor to trigger the onset of a disorder); (2) a moderator role, modulating the expression of the disorder or directly shaping the environment of the child; or (3) the role of a dependent variable, itself altered by anxiety (Lonigan & Phillips, 2001).

Anxiety sensitivity (AS) is a controversial construct that refers to the "degree of displeasure" produced by the experience or the anticipation of anxiety. While some authors question the distinctiveness of this trait-like factor from TA or general fear (Lilienfeld, Turner, & Jacob, 1998), others argue that it is a qualitatively distinct phenomenon, both theoretically and empirically (McNally, 1996; Reiss, 1997). Without taking sides in this debate, we must note that AS was proved to be a specific predictor of anxiety disorders (but not of depression) in nonclinical samples (Hayward, Killen, Kraemer, & Taylor, 2000; Pollock, Carter, Dierker, Chazan-Cohen, & Merikangas, 2002; Schmidt, Lerew, & Jackson, 1997; Weems, Hammond-Laurence, Silverman, & Ginsburg, 1998). This specificity, together with the proof of genetic control of AS (Eley, Gregory, Clark, & Ehlers, 2007; Stein, Jang, & Livesley, 1999), suggests

13.2 Intrinsic vulnerability markers associated with childhood anxiety

DOMAIN	MARKER	CONCLUSIONS	DEVELOPMENTAL STUDIES
Temperament/ personality	Behavioral inhibition	There are specific associations between childhood inhibition and later anxiety disorders. Children of parents with anxiety disorders show increased behavioral inhibition.	Biederman et al., 1990, 1993; Hirshfeld et al., 1992; Beidel & Turner, 1997; Rosenbaum et al., 1991; Prior et al., 2000; Lonigan et al., 1994; Joiner et al., 1996; Lonigan et al., 1999; Ţincaş et al., 2007; Muris & Ollendick, 2005; Caspi et al., 1995; Schmidt et al., 1997; Pollock et al., 2002; Hayward et al., 2000
	Negative affectivity/ neuroticism	Maternal ratings of shyness in late childhood are associated with anxiety disorders in adolescence.	
	Low effortful control	General risk for psychopathology, including anxiety and depression *or* specific concurrent or predictive associations with anxiety symptoms/ disorders.	
	Lack of control, inhibition, sluggishness	In combination with high neuroticism, low effortful control can predispose the individual to internalizing disorders.	
	Anxiety, sensitivity	At age 5, lack of control and inhibition were predictors of anxiety in boys, and lack of control and sluggishness in girls. Anxiety and sensitivity are specific predictors of anxiety disorders (especially panic attacks).	
Autonomic reactivity and psychophysiologic responses	Heart rate Heart period variability	Under conditions of novelty/stress, children with behavioral inhibition or anxiety disorders exhibit a shift from parasympathetic to sympathetic control (increase in heart rate, reduction in high frequency components of heart period variability).	Kagan, 1995; Rogeness et al., 1990; Shalev et al.,1998; Merikangas et al., 1999; Grillon et al., 1997; Kagan, 1995
	Skin conductance	Enhanced cardiovascular activity following an accident predicted PTSD. Fearlessness (modeled by skin conductance) is associated with low anxiety and behavior problems.	
	Startle reflex abnormalities	Startle reflex abnormalities have been found in children of adults with anxiety or in inhibited children at risk for anxiety disorders.	

(*continued*)

13.2 Intrinsic vulnerability markers associated with childhood anxiety *(continued)*

DOMAIN	MARKER	CONCLUSIONS	DEVELOPMENTAL STUDIES
Ventilatory function	Sensitivity to respiratory perturbation	Increased CO_2 sensitivity in children with anxiety disorders. Abnormalities in respiration as revealed by smoking in adolescents predispose to later anxiety.	Pine et al., 2000; Breslau & Klein, 1999; Johnson et al., 2000
Neurochemical and Neurohormonal	Salivary cortisol (index of greater responsivity of the HPA axis)	When compared to extremely uninhibited children, extremely anxious preschoolers have higher morning cortisol levels. In children attending full-day day care, shyness and sadness were positively correlated with cortisol elevations from morning to afternoon.	Schmidt et al., 1997; Kagan et al., 1987; Dettling et al., 1999; Tout et al., 1998; Sallee et al., 2000
	Noradrenergic system	Manipulations of the noradrenergic system have been shown to selectively elevate anxiety symptoms in children with anxiety disorders.	

that AS might represent a "potential endophenotype for childhood panic/somatic symptoms in molecular genetic research" (Gregory & Eley, 2007, p. 208).

Second, anxiety symptoms/disorders in children and adolescents have also been associated with a specificity of autonomic responses to threatening stimuli (heart rate, heart period variability, blood pressure, and catecholamine levels), psychophysiological reactions (skin conductance, pupil dilatation, startle reflex), and particular aspects in the ventilatory function (sensitivity to respiratory stimulation via inhaled CO_2 or lactate infusion). Some of these perturbations appear to be specific to certain (especially acute) emotional states, but the direction of the influence (anticipatory or as a downstream manifestation of anxiety states) remains uncertain (Merikangas & Pine, 2002).

Finally, specific neurochemical alterations have been found to be predictive or associated with anxiety disorders. While manipulations of the serotonergic system or the noradrenergic system have mostly been conducted in animal models or in the case of adult participants (see Sallee et al., 2000, for an exception), some studies with children have demonstrated the alterations in the hypothalamic-pituitary-adrenal (HPA) axis regulation, as revealed by elevated cortisol levels in the case of anxiety disorders.

AN INFORMATION-PROCESSING APPROACH TO CHILDHOOD ANXIETY

So far, we have reviewed the early vulnerability markers of anxiety disorders with little clarification of their involvement in the generation or maintenance of these disorders. The genetic, temperamental, or psychophysiological predispositions should be related to the neural circuitry underlying anxious behavior and, ultimately, to the cognitive functioning of a child with anxiety. Information-processing frameworks focus on the cognitive biases and distortions characteristic of childhood anxiety and attempt to model the sequence of steps involved in the generation, maintenance, and modification of

information through the cognitive system (see Alfano, Beidel, & Turner, 2002; Daleiden & Vasey, 1997; Pine, 2007; Vasey & MacLeod, 2001). Only recently have such frameworks attempted to integrate findings from neuroscience that are of direct relevance to the processes involved in anxious thoughts and behaviors (e.g., Pine, 2007; Telzer, Mogg, Bradley, Mai, Ernst, Pine, & Monk, 2008).

In the information-processing framework outlined by Pine (2007), he explicitly argues that it is difficult to provide matches between clinical criteria for a disorder and constructs from neuroscience. Neural function has been related to ongoing information-processing operations, rather than to static clinical criteria. He proposes an alternative view, which we describe here, as it forms the basis for our review of neurocognitive functioning in childhood anxiety. Genetic and environmental influences shape the underlying neural circuitry (Factor 1), which itself does not map directly onto anxiety phenotypes but rather affects the way information is being processed (Factor 2). This information processing translates into anxiety disorders, anxiety dimensions (state-trait, subclinical features, neuroticism), or temperamental predispositions (high reactivity, behavioral inhibition; Factor 3). We have so far discussed the genetic and environmental influences acting upon Factor 1, and their distal outcome (Factor 3); it is now time to analyze the pathways between specific neuroscience findings and cognitive functioning in children with anxiety. We will follow the same tripartite focus upon groups of cognitive processes relevant to pediatric anxiety as that used in Pine's the framework and will refer to (1) threat-attention capture, (2) threat appraisal, and (3) memory and learning. This type of study emerged in the late 1990s, with an initial focus on the controversial results of attempts to replicate the attentional and inferential biases found in adults among children and adolescents, and has progressed through a refinement of tasks and the search for neural correlates of these processes.

Attention to Threat

In adults, it is a generally accepted (and widely documented) fact that stimuli corresponding to specific threat-related concerns of the anxious individual consume increased attentional resources (see Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & van IJzendoorn, 2007, for a recent comprehensive meta-analysis). This has been proved especially regarding (1) the orienting component of attention, through use of the Posner-orienting or the dot-probe paradigm, and (2) attention orienting and regulation, through use of the emotional Stroop. Developmental research has generally followed the same tracks, but the results have been conflictual in revealing a bias toward or away from threatening stimuli; moreover, some studies have failed to show any anxiety-specific bias regarding these stimuli.

Simple detection of threatening faces was proved to be faster in typical children 7–10 years of age (Hadwin, Donnelly, French, Richards, Watts, & Daley, 2003). Studies using modified versions of the Stroop task to include threat-related verbal or pictorial stimuli have found either longer latencies on these stimuli in anxious children (Martin, Horder, & Jones, 1992; Martin & Jones, 1995—for children 4–13 years old in both studies) or a nonspecific effect of concern-related stimuli, irrespective of anxiety group (Kindt, Brosschot, & Everaerd, 1997; Mogg, Mathews, Bird, & MacGregor-Morris, 1990). Analyzing the reasons for these inconsistencies, Vasey and MacLeod (2001) conclude, "The modified Stroop task has proven to be an unreliable method of demonstrating attentional bias to feared stimuli in children suffering from specific fears" (p. 261). This lack of an effect was found in relation to not only the outcome of anxiety disorders, but also the temperamental dimension of anxiety. Schwartz, Snidman, and Kagan (1996) and Kagan, Snidman, Zentner, and Peterson (1999) found no slowing in inhibited children (or children who had been inhibited as toddlers) related to the threat words. An interesting finding was the strong effect of trauma-related words in children suffering from PTSD, and even in children who had a parent suffering from PTSD (Moradi, Taghavi, Neshat Doost, Yule, & Dalgleish, 1999).

Studies using probe detection tasks have subjects identify the targets in certain target spatial positions that replace threat-related stimuli; the capture of attention is measured by the latency to identify these targets. This type of study has been much more consistent in confirming the presence of an anxiety-linked effect in anxious children and youths. Some have shown an attentional bias toward the threatening stimuli in clinical and nonclinical populations of children as a function of TA (Heim-Dreger, Kohlmann, Eschenbeck, & Burkhardt, 2006; Schippell, Vasey, Cravens-Brown, & Bretveld, 2003; Telzer et al., 2008; Vasey, Daleiden, Williams, & Brown, 1995—only in older children), but not of state anxiety (Vasey, El-Hag, & Daleiden, 1996). Neuroimaging results (e.g., Telzer et al., 2008) revealed an association between TA and the right dorsolateral prefrontal cortex (PFC) on the contrast of trials reflecting attentional bias toward angry faces, and between TA and right ventrolateral PFC on all trials with face stimuli,

S___
E___
L___

irrespective of emotional content. Monk et al. (2006) also used a visual probe task in adolescents with GAD and revealed an attention bias away from angry faces, correlating with an enhanced activation of the right ventrolateral PFC in response to the angry facial expressions. The specific activation of lateral PFC areas only in the case of TA, areas associated with increased cognitive control, may suggest an association between TA and greater processing needs in performance of the task and reflects the interplay between threat detection and threat appraisal, an issue that will be further stressed throughout this section.

Regarding developmental trends, studies have generally failed to reveal anxiety-linked attentional biases in children younger than 7–12 years of age (Vasey & MacLeod, 2001); prior to that age, studies reveal a non-anxiety-specific bias toward threatening stimuli in all children (Vaish, Grossman, & Woodward, 2008). An interesting related finding is the fact that healthy adolescents have an orienting bias toward threat where healthy adults show no such preference, and anxious adolescents display avoidance where anxious adults display vigilance (Monk et al., 2006). Pine (2007) considers this to be a proof of a maturational increase in the threshold for threats affecting attention orienting. The developmental question is most relevant: how and when does the association between anxiety and selective attention become specialized? The search for the earliest predictors of childhood anxiety might benefit from further refinement of methodological tools that might not confound, for instance, the targeted effect of stimuli valence with overall inhibitory demands (such as the ones from the Stroop task, which might be too difficult altogether for very young children).

The neural bases for the attention biases include the amygdala, which plays a role in the detection of and response to threat-related cues and the PFC in modulating this attention bias (Bishop, 2007; Monk et al., 2006). Studies investigating amygdala dysfunction in pediatric anxiety have revealed both structural modifications (increased size, see de Bellis et al., 2000; decreased size, see Millham, Nugent, Drevets, Leibenluft, Ernst, Charney, & Pine, 2005) and functional hyperactivation (in the case of fearful faces, see Thomas et al., 2001; in previously inhibited children, see Schwartz, Wright, Shin, Kagan, & Rauch, 2003).

Threat Appraisal

An interpretative bias that appears in later explicit stages of stimulus classification has been more consistently documented in children. After the initial automatic classification of stimuli, a more elaborated iterative appraisal process assigns meaning to the stimulus according to the individual's goals. A correlation between level of TA and the interpretation of ambiguous stimuli as threatening has been found by several studies using pictorial stimuli (in children 7–9 years old by Hadwin, Frost, French, & Richards, 1997; in children and adolescents 9–16-years old by Taghavi, Moradi, Neshat-Doost, Yule, & Dalgleish, 1999) and vignettes and stories (Barrett et al., 1996; Bell-Dolan, 1995; Bogels & Zigterman, 2000; Chorpita, Albano, & Barlow, 1996; Muris, Kindt, Bögels, Merckelbach, Gadet, & Moulaert, 2000). Beyond these biased interpretations relative to controls, children with anxiety have also been shown to present more negative anticipations of future events (Magnusdottir & Smari, 1999; Spence, Donova, & Brechman-Toussaint, 1999). Interestingly, this is indirectly reflected by their maladaptive, usually avoidant coping styles (Barrett et al., 1996; Chorpita et al., 1996; Bell-Dolan, 1995; Vasey, Daleiden, & Williams, 1992). Not only verbal reports but also some defensive reflexes (autonomic, electromyographic, respiratory, and oculomotor) could be used in inferring threat appraisal in children and youths (e.g., Pine, Klein, Roberson-Nay, Mannuzza, Moulton, Woldehawariat, & Guardino, 2005).

Regarding the disorder specificity of these appraisal biases, dissociation was found in the responses to specific stimuli in the case of SAD and social phobia. While SAD-diagnosed adolescents manifest appraisal biases for respiratory threats, youths with social phobia are biased in their appraisal of social threats, and not vice versa (Pine et al., 2005).

There are certain developmental trends in the processes of threat appraisal, especially regarding the hierarchy of elements: while children classify specific objects as threatening, adolescents tend to classify broader classes of stimuli (e.g., all public speech contexts) as menacing. This is probably the result of their cognitive and linguistic development, which allows for more elaborated scenarios and complex classifications of threats and of threat-related responses. This change is backed up by modifications in the neural circuitry related to threat appraisal, comprising the ventral PFC and the posterior temporal cortex, which play a role in the evaluation of stimulus salience (Pine, 2007). Monk et al. (2006) found enhanced activity in ventrolateral PFC when young participants were performing a threat dot-probe task. McClure et al. (2007) found that adolescents with GAD presented a facilitation of amygdala activation, combined with ventral and medial PFC engagement, when making threat appraisals for facial expressions.

Memory and Learning

The cognitive distortions at the memory and learning level have been investigated far less in children, partially as a consequence of the inconsistent results obtained from the investigation of emotional memory biases in adults (Mathews, Mackintosh, & Fulcher, 1997; Miu et al., 2005). However, a review of short-term and working memory functioning in anxious children (Visu-Petra, Ciairano, & Miclea, 2006) found proof for the detrimental effect of anxiety upon verbal memory (especially in conditions with high load) in tasks involving emotionally neutral stimuli. At the basic level of short-term memory, the microanalysis of preschoolers' responses in verbal memory span tasks (Visu-Petra, Miclea, Cheie, & Benga, 2008) revealed the predictive effect of nonclinical TA, which was marginal for performance accuracy (number of recalled items) and more consistent for performance efficiency (longer durations of preparatory intervals and of inter-word pauses). The results were interpreted in the framework of the attentional control theory (M. W. Eysenck et al., 2007), suggesting that anxiety primarily affects processing efficiency. Only if anxious subjects cannot compensate by investing supplementary time/resources involved (e.g., conditions of high load) will a detrimental effect of anxiety upon accuracy be visible. In the same conceptual framework, Owens, Stevenson, Norgate, and Hadwin (2008) found that verbal working memory performance significantly mediated the relationship between TA and academic performance in adolescent's age 11–12 years. When clinical child samples were investigated, verbal and visual memory deficits predicted future anxiety disorders (Pine et al., 1999), correlated with the presence of SAD and overanxious disorder (Toren et al., 2000), and were specific to major depressive disorder, but not social phobia and GAD (Gunther, Holtkamp, Jolles, Herpertz-Dahlmann, & Konrad, 2004). Finally, Vasa et al. (2007) showed that children and adolescents with social phobia had reduced visual but not verbal memory scores.

Data regarding emotional memory in childhood anxiety have been inconsistent or negative (Vasa et al., 2007). Using word lists, Daleiden (1998) found evidence of a memory bias favoring negative verbal information (only conceptual, not perceptual) in trait anxious eighth-grade children. He interprets the results as proof of the deficit in using attentional disengagement as an emotional regulatory skill in children with high levels of anxiety. Visu-Petra, Ţincaş, Cheie, and Benga (in press) found that preschoolers with high trait anxiety are slower in a memory updating task, and are differentially influenced by the emotional valence of the facial expressions than their low-anxious counterparts. More specific, they were slower and less accurate in detecting and remembering happy faces, and more accurate in response to angry faces. In a clinical sample, Pine, Lissek, Klein, Mannuzza, Moulton, Guardino, and Woldehawariat (2004) used a face memory paradigm and found that anxiety disorders did not predict memory performance. Ladouceur, Dahl, Williamson, Birmaher, Ryan, and Casey (2005) used an emotional *n*-back task in a mixed clinical sample; no significant interference of negative pictures was found on the memory performance of the anxiety group.

Regarding the neurobiological underpinnings of the anxiety-memory relationship, studies with adult participants have suggested that non-emotional memory deficits might reflect dysfunctions in the medial temporal lobe, a region that is implicated in both anxiety and memory (Charney, 2003; Vasa et al., 2007). A second hypothesis relates to the secondary nature of the memory dysfunctions, which emerge as a consequence of biased attentional processes.

There is an unfortunate research tradition of studying these three types of anxiety-related cognitive biases separately. However, their confluence is obvious, because (1) appraisal is influenced by early automatic attentional capture and (2) both orienting and appraisal contribute to the encoding and subsequent processing of stimuli within memory systems. Empirically, there has been little explicit proof of this relationship in the case of childhood anxiety. Pine et al. (2005) have documented significant correlations between the time required for explicit threat appraisal and ratings of threat intensity. They suggest that appraisal biases may in fact emerge during development through interactions with attention, as children with automatic biases in stimulus detection might be expected to learn to classify stimuli as dangerous. An interesting research avenue would be investigating how learning might alter the attention-orienting and appraisal biases (Pine, 2007).

CLINICAL IMPLICATIONS: ASSESSMENT AND TREATMENT OF CHILDHOOD ANXIETY

The assessment process in childhood anxiety has mostly conformed to a clinical symptoms-based approach. However, as revealed throughout this chapter, in the past decades more and more studies have attempted to reveal the neurobiological and cognitive correlates that might help create a more comprehensive profile of these disorders. For very young ages, mostly symptoms

checklists with different informants (parents, teachers) have been used. In older children, structured diagnostic interviews and self-report measures are the preferential tools, which make use of the child as the best informant regarding his or her inner states and behaviors (see Schniering et al., 2000, for a review of instruments, with their advantages and problems). These instruments have either emphasized broad distinctions, such as the one between emotional (internalizing) and behavioral (externalizing) syndromes (Egger & Angold, 2006), or focused specifically on characterizing particular anxiety subtypes (e.g., Spence, Rapee, McDonald, & Ingram, 2001). We can refer the clinician to the comprehensive *Handbook of Infant, Toddler, and Preschool Mental Health Assessment* (DelCarmen-Wiggins & Carter, 2004) for a collection of instruments designed to assess anxiety disorders in early development.

A common underlying question that has been emphasized throughout this chapter relates to the clinical value of these vulnerability factors. Do they represent a specific underlying risk—and thus a potential target for anxiety prevention? Or are they simply overt expressions of anxiety disorders? Although we would be tempted to choose the first answer, there is some inconsistent evidence regarding their trait-like nature: threat-related biases appear amenable to change after therapy (e.g., orienting biases, Williams et al., 1996) or even after brief training exercises (MacLeod et al., 2002; Monk et al., 2004). Children's threat interpretations after intervention involving CBT plus parental involvement revealed significant decreases (Barrettt et al., 1996). Interestingly, this was not the case in the CBT-only intervention; this reveals the role of the parental environment in the maintenance of specific cognitive styles in anxious children (Alfano et al., 2002). Cognitive symptoms (negative cognitions and phobias) also decreased as a result of child and parent interventions for phobic children (Silverman, Kurtines, Ginsburg, Weems, Lumpkin, & Carmichael, 1999; Spence, Donovan, & Brechman-Toussaint, 2000). However, there appears to be a lack of specificity regarding the cognitive targets of the CBT interventions and the change mechanisms that they produce, with some studies producing the desired changes only through the use of behavioral, not cognitive, intervention (Beidel, Turner, & Morris, 1995).

Cognition has been examined as a causal factor in the development of anxiety in children (e.g., Kendall & Ronan, 1990) or as a moderator between specific vulnerabilities and anxiety (e.g., Chorpita & Barlow, 1998). As a possible mechanism for the transformation of an at-risk but unaffected individual to an individual with an anxiety disorder, Pine (2007) suggests "the development of heightened arousal for threats, emerging against a background of mild hypersensitivity to diverse threats" (p. 637). Intervention strategies (either externally mediated or discovered by at-risk children themselves) would target a more accurate differentiation between real and potential threats, although the hypersensitivity toward threat might remain constant throughout development. Departing from the traditional symptoms-based treatment (see Chorpita & Southam-Gerow, 2006, for a recent review of childhood anxiety treatments and outcomes), Daleiden and Vasey (1997) used the information-processing framework to suggest specific interventions targeting distinct stages of information processing. The strategies would aim to change early encoding by broadening the information that children attend to; correct interpretation biases and distortions; change anxious children's goals; or enhance response generation, selection, and enactment. These information-processing strategies would provide a complementary approach to the classical CBT treatment, increasing both the theoretical specificity of the intervention and the empirical validity of the outcomes.

Another developmental issue is the heterotypic continuity of the underlying vulnerability factors and of anxiety disorders themselves. Indeed, the review of vulnerability markers, especially in the information-processing framework, has revealed that nonclinical TA and clinical anxiety disorders present many similarities, supporting the view of an anxiety continuum. Moreover, anxiety itself often translates into other forms of psychopathology during development (especially anticipating depression), suggesting a larger psychopathology continuum. Any analysis of these metamorphoses should take into account the development of cognitive and regulatory processes involved in anxiety. The lack of a consistent and identifiable anxiety-related effect upon cognition prior to 7 years of age might only be a result of children's lack of the cognitive skills to report cognitive contents or to comply with task demands (Alfano et al., 2002), or a reflection of specific early deficits in emotion understanding among anxious children (Southam-Gerow & Kendall, 2000). Self-appraisal and self-descriptions are also more related to physical standards before the age of 8 (Vasey, 1993), as younger children have difficulties in social comparisons.

As Pine (2007) suggests, clinicians hoped that by extracting specific clusters of symptoms that resulted in categorical definitions of anxiety, they could "carve nature at its joints, identifying syndromes closely linked to brain dysfunction" (p. 632). However, the multiple types of evidence brought together in this chapter (prevalence and comorbidity, genetic, developmental,

from cognitive psychology and neuroscience) lead to questions about the specificity and differentiation of the clinical syndromes, suggesting the need for an alternative classification closer to brain function and dysfunction (i.e., endophenotypes).

ACKNOWLEDGEMENTS

Preparation of this paper was partially supported by a National University Research Council Grant, CNCSIS 2440/2008.

REFERENCES

Achenbach, T. M. (1985). *Assessment and taxonomy of child and adolescent psychopathology.* Beverly Hills, CA: Sage.

Alden, L. E., & Taylor, C. T. (2004). Interpersonal processes in social phobia. *Clinical Psychology Review, 24*(7), 857–882.

Alessi, N., & Magen, J. (1988). Panic disorder in psychiatrically hospitalized children. *American Journal of Psychiatry, 145,* 1450–1452.

Alfano, C. A., Beidel, D. C., & Turner, S. M. (2002). Cognition in childhood anxiety: Conceptual methodological and developmental issues. *Clinical Psychology Review, 22,* 1209–1238.

Allen, N. B., Lewinsohn, P. M., & Seeley, J. R. (1998). Prenatal and perinatal influences on risk for psychopathology in childhood and adolescence. *Development and Psychopathology, 10,* 513–529.

Alonso, J., & Lepine, J. P. (2007). Overview of key data from the European Study of the Epidemiology of Mental Disorders (ESEMeD). *Journal of Clinical Psychiatry, 68*(Suppl. 2), 3–9.

American Psychiatric Association. (1968). *Diagnostic and statistical manual for mental disorders* (2nd ed.). Washington, DC: Author.

American Psychiatric Association (1980). *Diagnostic and statistical manual for mental sisorders* (3rd ed.). Washington, DC: Author.

American Psychiatric Association (1994). *Diagnostic and statistical manual for mental disorders* (4th ed.). Washington DC: Author.

Amstadter, A. (2008). Emotion regulation and anxiety disorders. *Journal of Anxiety Disorders, 22*(2), 211–221.

Andor, T., Gerlach, A. L., & Rist, F. (2008). Superior perception of phasic physiological arousal and the detrimental consequences of the conviction to be aroused on worrying and metacognitions in GAD. *Journal of Abnormal Psychology, 117*(1), 193–205.

Andrews, G. (1996). Comorbidity in neurotic disorders: The similarities are more important than the differences. In R. M. Rapee (Ed.), *Current controversies in the anxiety disorders* (pp. 3–20). New York: Guilford Press.

Arbelle, S., Benjamin, J., Golin, M., Kremer, I., Belmaker, R. H., & Ebstein, R. P. (2003). Relation of shyness in grade schoolchildren to the genotype for the long form of the serotonin transporter promoter region polymorphism. *American Journal of Psychiatry, 160,* 671–676.

Armsden, G. C., McCauley, E., Greenberg, M. T., Burke, P. M., & Mitchell, J. R. (1990). Parent and peer attachment in early adolescent depression. *Journal of Abnormal Child Psychology,* 18, 683–697.

Baekken, P. M., Skorpen, F., Stordal, E., Zwart, J. A., & Hagen, K. (2008). Depression and anxiety in relation to catechol-O-methyltransferase Val158Met genotype in the general population: The Nord-Trondelag Health Study (HUNT). *BMC Psychiatry, 8,* 48.

Bar-Haim, Y., Lamy, D., Pergamin, L., Bakermans-Kranenburg, M. J., & van IJzendoorn, M. H. (2007). Threat-related attentional bias in anxious and non-anxious individuals: A meta-analytic study. *Psychological Bulletin, 133,* 1–24.

Barrett, P. M., Dadds, M., & Rapee, R. (1996). Family treatment of childhood anxiety: A controlled trial, *Journal of Consulting and Clinical Psychology, 64,* 333–342.

Barrett, P. M., Rapee, R. M., Dadds, M. R., & Ryan, S. M. (1996). Family enhancement of cognitive style in anxious and aggressive children. *Journal of Abnormal Child Psychology, 37, 187*–203.

Battaglia, M., Ogliari, A., Zanoni, A., Citterio, A., Pozzoli, U., Giorda, R., et al. (2005). Influence of the serotonin transporter promoter gene and shyness on children's cerebral responses to facial expressions. *Archives Of General Psychiatry, 62,* 85–94.

Bechara, A., Damasio, A. R., Damasio, H., & Anderson, S. W. (1994). Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition, 50*(1–3), 7–15.

Beck, A. T. (1976). *Cognitive therapy and the emotional disorders.* New York: International Universities Press.

Beck, A. T., & Clark, D. A. (1997). An information processing model of anxiety: Automatic and strategic processes. *Behaviour Research and Therapy, 35*(1), 49–58.

Beck, A. T., Emery, G., & Greenberg, R. (1985). *Anxiety disorders and phobias: A cognitive perspective.* New York: Basic Books.

Beck, R., & Perkins, T. S. (2001). Cognitive content-specificity for anxiety and depression: A meta-analysis. *Cognitive Therapy and Research, 25*(6), 651–663.

Beidel, D. C., Flink, C. M., & Turner, S. M. (1996). Stability of anxious symptomatology in children. *Journal of Abnormal Child Psychology, 24,* 257–269.

Beidel, D. C., Silverman, W., & Hammond-Laurence, K. (1996). Overanxious disorder: Subsyndromal state or specific disorder? A comparison of clinic and community samples. *Journal of Clinical Child Psychology, 25,* 25–32.

Beidel, D. C., & Turner, S. M. (1997). At risk for anxiety: I. Psychopathology in the offspring of anxious parents. *Journal of the American Academy of Child & Adolescent Psychiatry, 36,* 918–924.

Beidel, D. C., Turner, S. M., & Morris, T. L. (1995). A new inventory to assess childhood social anxiety and phobia: The Social Phobia and Anxiety Inventory for Children. *Psychological Assessment, 7,* 73–79.

Bell-Dolan, D. J. (1995). Social cue interpretation of anxious children. *Journal of Clinical Child Psychology, 24,* 1–10.

Bernstein, G. A., Garfinkel, B. D., & Hoberman, H. M. (1989). Self-reported anxiety in adolescents. *American Journal of Psychiatry, 146,* 384–386.

Biederman, J., Rosenbaum, J. F., Bolduc-Murphy, E. A., Faraone, S. V., Chaloff, J., Hirshfeld, D. R., & Kagan, J. (1993). A 3-year

S___
E___
L___

follow-up of children with and without behavioral inhibition. *Journal of the American Academy of Child & Adolescent Psychiatry, 32,* 814–821.

Biederman, J., Rosenbaum, J. F., Hirshfeld, D. R., & Faraone, S. V. (1990). Psychiatric correlates of behavioral inhibition in young children of parents with and without psychiatric disorders. *Archives of General Psychiatry, 47,* 21–26.

Bienvenu, O. J., & Ginsburg, G. S. (2007). Prevention of anxiety disorders. *International Review of Psychiatry, 19*(6), 647–654.

Bishop, S. J. (2007). Neurocognitive mechanisms of anxiety: An integrative account. *Trends in Cognitive Science, 11,* 307–316.

Blanchard, D. C., & Blanchard, R. J. (1990). Behavioral correlates of chronic dominance-subordination relationships of male rats in a seminatural situation. *Neuroscience Biobehavioral Review, 14*(4), 455–462.

AuQ2 Blanchette, I., & Richards, A. (2003). Anxiety and the interpretation of ambiguous information: beyond the emotion-congruent effect. *J Exp Psychol Gen, 132*(2), 294–309.

Blanchette, I., Richards, A., & Cross, A. (2007). Anxiety and the interpretation of ambiguous facial expressions: The influence of contextual cues. *Quarterly Journal of Experimental Psychology, 60*(8), 1101–1115.

Blechert, J., Michael, T., Grossman, P., Lajtman, M., & Wilhelm, F. H. (2007). Autonomic and respiratory characteristics of posttraumatic stress disorder and panic disorder. *Psychosomatic Medicine, 69*(9), 935–943.

Bleil, M. E., Gianaros, P. J., Jennings, J. R., Flory, J. D., & Manuck, S. B. (2008). Trait negative affect: Toward an integrated model of understanding psychological risk for impairment in cardiac autonomic function. *Psychosomatic Medicine, 70*(3), 328–337.

Blumenthal, T. D., Cuthbert, B. N., Filion, D. L., Hackley, S., Lipp, O. V., & Van Boxtel, A. (2005). Committee report: Guidelines for human startle eyeblink electromyographic studies. *Psychophysiology, 42*(1), 1–15.

Bogels, S. M., & Zigterman, D. (2000). Dysfunctional cognitions in children with social phobia, separation anxiety disorder, and generalized anxiety disorder. *Journal of Abnormal Child Psychology, 28,* 205–211.

Bolton, D., Eley, T. C., O'Connor, T. G., Perrin, S., Rabe-Hesketh, S., Rijsdijk, F., et al. (2006). Prevalence and genetic and environmental influences on anxiety disorders in 6-year-old twins. *Psychological Medicine, 36,* 335–344.

Borkovec, T. D., & Roemer, L. (1995). Perceived functions of worry among generalized anxiety disorder subjects: Distraction from more emotionally distressing topics? *Journal of Behavior Therapy in Experimental Psychiatry, 26*(1), 25–30.

Bradley, B. P., Mogg, K., & Lee, S. C. (1997). Attentional biases for negative information in induced and naturally occurring dysphoria. *Behaviour Research and Therapy, 35*(10), 911–927.

Bradley, B. P., Mogg, K., & Williams, R. (1994). Implicit and explicit memory for emotional information in non-clinical subjects. *Behaviour Research and Therapy, 32*(1), 65–78.

Brady, E. U., & Kendall, P. C. (1992). Comorbidity of anxiety and depression in children and adolescents. *Psychological Bulletin, 111,* 244–255.

Brandes, M., & Bienvenu, O. J. (2006). Personality and anxiety disorders. *Current Psychiatry Reports, 8*(4), 263–269.

Braun, C., Kowallik, P., Freking, A., Hadeler, D., Kniffki, K. D., & Meesmann, M. (1998). Demonstration of nonlinear components in heart rate variability of healthy persons. *American Journal of Physiology, 275*(5 Pt 2), H1577–1584.

Brendle, J. R., & Wenzel, A. (2004). Differentiating between memory and interpretation biases in socially anxious and nonanxious individuals. *Behaviour Research and Therapy, 42*(2), 155–171.

Breslau, N., & Klein, D. F. (1999). Smoking and panic attacks: An epidemiologic investigation, *Archives of General Psychiatry, 56,* 1141–1147.

Brewin, C. R., & Holmes, E. A. (2003). Psychological theories of posttraumatic stress disorder. *Clinical Psychology Review, 23*(3), 339–376.

Brown, S. M., & Hariri, A. R. (2006). Neuroimaging studies of serotonin gene polymorphisms: Exploring the interplay of genes, brain, and behavior. *Cognitive, Affective, and Behavioral Neuroscience, 6*(1), 44–52.

Brown, S. M., Peet, E., Manuck, S. B., Williamson, D. E., Dahl, R. E., Ferrell, R. E., et al. (2005). A regulatory variant of the human tryptophan hydroxylase-2 gene biases amygdala reactivity. *Molecular Psychiatry, 10*(9), 884–888, 805.

Brown, T. A., Barlow, D. H., & Liebowitz, M. R. (1994). The empirical basis of generalized anxiety disorder. *American Journal of Psychiatry, 151*(9), 1272–1280.

Brown, T. A., Di Nardo, P. A., Lehman, C. L., & Campbell, L. A. (2001). Reliability of DSM-IV anxiety and mood disorders: Implications for the classification of emotional disorders. *Journal of Abnormal Psychology, 110*(1), 49–58.

Buckholtz, J. W., Callicott, J. H., Kolachana, B., Hariri, A. R., Goldberg, T. E., Genderson, M., et al. (2008). Genetic variation in MAOA modulates ventromedial prefrontal circuitry mediating individual differences in human personality. *Molecular Psychiatry, 13*(3), 313–324.

Buckley, P. J., Michels, R., & Mackinnon, R. A. (2006). Changes in the psychiatric landscape. *American Journal of Psychiatry, 163*(5), 757–760.

Buckley, T. C., Blanchard, E. B., & Hickling, E. J. (2002). Automatic and strategic processing of threat stimuli: A comparison between PTSD, panic disorder, and nonanxiety controls. *Cognitive Therapy and Research, 26*(1), 97–115.

Buckley, T. C., Blanchard, E. B., & Neill, W. T. (2000). Information processing and PTSD: A review of the empirical literature. *Clinical Psychology Reviews, 20*(8), 1041–1065.

Butler, G., Fennell, M., Robson, P., & Gelder, M. (1991). Comparison of behavior therapy and cognitive behavior therapy in the treatment of generalized anxiety disorder. *Journal of Consulting and Clinical Psychology, 59*(1), 167–175.

Calvo, M. G., Avero, P., & Miguel-Tobal, J. J. (2003). Multidimensional anxiety and Content-specificity Effects in Preferential Processing of Threat. *European Psychologist, 8*(4), 252–265.

Campbell, M. J., Schmidt, L. A., Santesso, D. L., Van Ameringen, M., Mancini, C. L., & Oakman, J. M. (2007). Behavioral and psychophysiological characteristics of children of parents with social phobia: A pilot study. *International Journal of Neuroscience, 117*(5), 605–616.

Canli, T., Amin, Z., Haas, B., Omura, K., & Constable, R. T. (2004). A double dissociation between mood states and personality traits in the anterior cingulate. *Behavioral Neuroscience, 118*(5), 897–904.

___S
___E
___L

Canli, T., Congdon, E., Gutknecht, L., Constable, R. T., & Lesch, K. P. (2005). Amygdala responsiveness is modulated by tryptophan hydroxylase-2 gene variation. *Journal of Neural Transmission, 112*(11), 1479–1485.

Canli, T., & Lesch, K. P. (2007). Long story short: The serotonin transporter in emotion regulation and social cognition. *Nature Neuroscience, 10*(9), 1103–1109.

Cantwell, D. P., & Baker, L. (1987). Prevalence and type of psychiatric disorder and developmental disorders in three speech and language groups. *Journal of Communication Disorders, 20,* 151–160.

Cantwell, D. P., & Baker, L. (1989). Stability and natural history of DSM-III childhood diagnoses. *Journal of the American Academy of Child & Adolescent Psychiatry, 28,* 691–700.

Carey, G., & Gottesman, I. I. (1981). Twin and family studies of anxiety, phobic, and obsessive disorders. In D. F. Klein & E. Rabkin (Eds.), *Anxiety: New research and concepts* (pp. 117–136). New York: Raven Press.

Carlson, E., & Sroufe, L. A. (1995). The contribution of attachment theory to developmental psychopathology. In D. Cicchetti & D. Cohen (Eds.), *Developmental processes and psychopathology: Vol. 1. Theoretical perspectives and methodological approaches.* New York: Cambridge University Press.

Cartwright-Hatton, S., McNicol, K., & Doubleday, E. (2006). Anxiety in a neglected population: Prevalence of anxiety disorders in pre-adolescent children. *Clinical Psychology Review, 26,* 817–833.

Casey, L. M., Oei, T. P., & Newcombe, P. A. (2004). An integrated cognitive model of panic disorder: The role of positive and negative cognitions. *Clinical Psychology Review 24*(5), 529–555.

Caspi, A., Henry, B., McGee, R. O., Moffitt, T. E., & Silva, P. A. (1995).Temperamental origins of child and adolescent behavior problems: From age three to age fifteen. *Child Development, 66,* 55–68.

Caspi, A., Moffitt, T. E., Newman, D. L., & Silva, P. A. (1996). Behavioral observations at age 3 years predict adult psychiatric disorders. *Archives of General Psychiatry, 53,* 1033–1039.

Caspi, A., Sugden, K., Moffitt, T. E., Taylor, A., Craig, I. W., Harrington, H., et al. (2003). Influence of life stress on depression: Moderation by a polymorphism in the 5-HTT gene. *Science, 301*(5631), 386–389.

Caspi, A., Taylor, A., Moffitt, T. E., & Plomin, R. (2000). Neighborhood deprivation affects children's mental health: Environmental risks identified in a genetic design. *Psychological Science, 11*(4), 338–342.

Cattell, R. B., & Scheier, I. H. (1958). The nature of anxiety: A review of thirteen multivariate analyses comprising 814 variables. *Psychological Reports, 4,* 351–388.

Charney, D. S. (2003). Neuroanatomical circuits modulating fear and anxiety behaviors. *Acta Psychiatrica Scandinavica, 108*(Suppl. 417), 38–50.

Chorpita, B. F., Albano, A. M., & Barlow, D. H. (1996). Cognitive processing in children: Relationship to anxiety and family influences. *Journal of Clinical Child Psychology, 25,* 170–176.

Chorpita, B. F., Albano, A.M., Heimberg, R. G., & Barlow, D. H. (1996). A systematic replication of the prescriptive treatment of school refusal behavior in a single subject. *Journal of Behavior Therapy and Experimental Psychiatry, 27,* 281–290.

Chorpita, B. F., & Barlow, D. H. (1998). The development of anxiety: The role of control in the early environment. *Psychological Bulletin, 124,* 3–21.

Chorpita, B. F., & Southam-Gerow, M. (2006). Fears and anxieties. In E. J. Mash & R. A. Barkley (Eds.), *Treatment of child disorders* (3rd ed., pp. 271–335). New York: Guilford Press.

Cicchetti, D., & Rogosh, F. A. (1996). Equifinality and multifinality in developmental psychopathology. *Development and Psychopathology, 8,* 597–600.

Clark, D. M. (1986). A cognitive approach to panic. *Behaviour Research and Therapy, 24*(4), 461–470.

Clark, D. M., & Wells, A. (1995). A cognitive model of social phobia. In R. Heimberg, M. Liebowitz, D. A. Hope & F. R. Schneider (Eds.), *Social phobia: Diagnosis, assessment and treatment* (pp. 69–93). New York: Guilford Press.

Clark, L. A. (2005). Temperament as a unifying basis for personality and psychopathology. *Journal of Abnormal Psychology, 114,* 505–521.

Clark, L. A., & Watson, D. (1991). Tripartite model of anxiety and depression: Psychometric evidence and taxonomic implications. *Journal of Abnormal Psychology, 100,* 316–336.

Cloitre, M., & Liebowitz, M. (1991). Memory bias in panic disorder: An investigation of the cognitive avoidance hypothesis. *Cognitive Therapy and Research, 15,* 371–386.

Cohen, H., Matar, M. A., Kaplan, Z., & Kotler, M. (1999). Power spectral analysis of heart rate variability in psychiatry. *Psychotherapy and Psychosomatics, 68*(2), 59–66.

Coles, M. E., & Heimberg, R. G. (2002). Memory biases in the anxiety disorders: Current status. *Clinical Psychology Review, 22*(4), 587–627.

Cornwell, B. R., Johnson, L., Berardi, L., & Grillon, C. (2006). Anticipation of public speaking in virtual reality reveals a relationship between trait social anxiety and startle reactivity. *Biological Psychiatry, 59*(7), 664–666.

Crisan, L.G., Pana S., Vulturar R., Heilman, R. M., Szekely, R., Druga, B., et al. (2009). Genetic contributions of the serotonin transporter to social learning of fear and economic decision making. *Social Cognitive and Affective Neuroscience* (e-pub ahead of print, June 17)

Cuthbert, B. N., Drobes, D., Patrick, C. J., & Lang, P. J. (1994). Autonomic and startle responding during affective imagery among anxious patients. *Psychophysiology, 31*(Suppl. 1), S37.

Cuthbert, B. N., Lang, P. J., Strauss, C., Drobes, D., Patrick, C. J., & Bradley, M. M. (2003). The psychophysiology of anxiety disorder: Fear memory imagery. *Psychophysiology, 40*(3), 407–422.

Daleiden, E. L. (1998). Childhood anxiety and memory functioning: A comparison of systemic and processing accounts. *Journal of Experimental Child Psychology, 68,* 216–235.

Daleiden, E. L., & Vasey, M. W. (1997). An information-processing perspective on childhood anxiety. *Clinical Psychology Review, 17,* 407–429.

Dalgleish, T. (1994). The relationship between anxiety and memory biases for material that has been selectively processed in a prior task. *Behaviour Research and Therapy, 32*(2), 227–231.

Dalgleish, T. (2004). Cognitive approaches to posttraumatic stress disorder: The evolution of multirepresentational theorizing. *Psychological Bulletin, 130*(2), 228–260.

Davidson, R. J. (2002). 2000 SPR Award for distinguished contributions to psychophysiology. *Psychophysiology, 39*(1), 1–8.

Davidson, R. J. (2003). Affective neuroscience and psychophysiology: Toward a synthesis. *Psychophysiology, 40*(5), 655–665.

S___
E___
L___

Davidson, R. J., Kalin, N. H., & Shelton, S. E. (1992). Lateralized effects of diazepam on frontal brain electrical asymmetries in rhesus monkeys. *Biological Psychiatry, 32*(5), 438–451.

Davidson, R. J., Marshall, J. R., Tomarken, A. J., & Henriques, J. B. (2000). While a phobic waits: Regional brain electrical and autonomic activity in social phobics during anticipation of public speaking. *Biological Psychiatry, 47*(2), 85–95.

Davis, M. (1998). Are different parts of the extended amygdala involved in fear versus anxiety? *Biological Psychiatry, 44*(12), 1239–1247.

de Bellis, M. D., Casey, B. J., Dahl, R. E., Birmaher, B., Williamson, D. E., Thomas, K. M., et al. (2000). A pilot study of amygdala volumes in pediatric generalized anxiety disorder. *Biological Psychiatry, 48,* 51–57.

de Jong, P., Visser, S., & Meckelback, H. (1996). Startle and spider phobia: Unilateral probes and the prediction of treatment effects. *Journal of Psychophysiology, 10,* 150–160.

DelCarmen-Wiggins, R., & Carter, A. (2004). *Handbook of infant, toddler, and preschool mental health assessment.* New York: Oxford University Press.

Demyttenaere, K., Bruffaerts, R., Posada-Villa, J., Gasquet, I., Kovess, V., Lepine, J. P., et al. (2004). Prevalence, severity, and unmet need for treatment of mental disorders in the World Health Organization World Mental Health Surveys. *Journal of the American Medical Association, 291*(21), 2581–2590.

Derryberry, D., & Reed, M. A. (2002). Anxiety-related attentional biases and their regulation by attentional control. *Journal of Abnormal Psychology, 111*(2), 225–236.

Dettling, A. C., Gunnar, M. R., & Donzella, B. (1999). Cortisol levels of young children in full-day childcare centers: Relations with age and temperament. *Psychoneuroendocrinology, 24,* 519–536.

Devineni, T., Blanchard, E. B., Hickling, E. J., & Buckley, T. C. (2004). Effect of psychological treatment on cognitive bias in motor vehicle accident-related posttraumatic stress disorder. *Journal of Anxiety Disorders, 18*(2), 211–231.

Di Nardo, P. A., Brown, T. A., & Barlow, D. H. (1994). *Anxiety Disorders Interview Schedule for DSM-IV—Lifetime version (ADIS-IV-L).* San Antonio, TX: Psychological Corporation.

Di Nardo, P., Moras, K., Barlow, D. H., Rapee, R. M., & Brown, T. A. (1993). Reliability of DSM-III-R anxiety disorder categories. Using the Anxiety Disorders Interview Schedule–Revised (ADIS-R). *Archives of General Psychiatry, 50*(4), 251–256.

Domschke, K., Ohrmann, P., Braun, M., Suslow, T., Bauer, J., Hohoff, C., et al. (2008). Influence of the catechol-O-methyltransferase val158met genotype on amygdala and prefrontal cortex emotional processing in panic disorder. *Psychiatry Research, 163*(1), 13–20.

Eaves, L. J., Silberg, J. L., Meyer, J. M., Maes, H. H., Simonoff, E., Pickles, A., et al. (1997). Genetics and developmental psychopathology: 2. The main effects of genes and environment on behavioral problems in the Virginia Twin Study of Adolescent Behavioral Development. *Journal of Child Psychology and Psychiatry, 38,* 965–980.

Eckberg, D. L. (1997). Sympathovagal balance: A critical appraisal. *Circulation, 96*(9), 3224–3232.

Egger, H. L., & Angold, A. (2006). Anxiety disorders. In J. Luby (Ed.), *Handbook of preschool mental health: Development, disorders, and treatment* (pp. 137–164). New York. Guilford Press.

Eley, T. C. (1999). Behavioral genetics as a tool for developmental psychology: Anxiety and depression in children and adolescents. *Clinical Child and Family Psychology Review, 2,* 21–36.

Eley, T. C. (2001). Genetic and environmental influences. In M. W. Vasey & M. R. Dadds (Eds.), *The developmental psychopathology of anxiety* (pp.45–59). Oxford: Oxford University Press.

Eley, T. C., Bolton, D., O'Connor, T. G., Perrin, S., Smith, P., & Plomin, R. (2003). A twin study of anxiety-related behaviours in pre-school children. *Journal of Child Psychology and Psychiatry, 44,* 945–960.

Eley, T. C., Gregory, A. M., Clark, D. M., & Ehlers, A. (2007). Feeling anxious: A twin study of panic/somatic symptoms, anxiety sensitivity and heart-beat perception in children. *Journal of Child Psychology and Psychiatry, 12,* 1184–1191.

Eley, T. C., & Stevenson, J. (1999). Using genetic analyses to clarify the distinction between depressive and anxious symptoms in children and adolescents. *Journal of Abnormal Child Psychology, 27,* 105–114.

Eley, T. C., Sugden, K., Gregory, A. M., Sterne, A., Plomin, R., & Craig, I. W. (2004). Gene-environment interaction analysis of serotonin system markers with adolescent depression. *Molecular Psychiatry, 9,* 908–918.

Endler, N. S., & Kocovski, N. L. (2001). State and trait anxiety revisited. *Journal of Anxiety Disorders, 15*(3), 231–245.

Ernst, M., & Paulus, M. P. (2005). Neurobiology of decision making: A selective review from a neurocognitive and clinical perspective. *Biological Psychiatry, 58*(8), 597–604.

Etkin, A., Egner, T., Peraza, D. M., Kandel, E. R., & Hirsch, J. (2006). Resolving emotional conflict: A role for the rostral anterior cingulate cortex in modulating activity in the amygdala. *Neuron, 51*(6), 871–882.

Etkin, A., Klemenhagen, K. C., Dudman, J. T., Rogan, M. T., Hen, R., Kandel, E. R., et al. (2004). Individual differences in trait anxiety predict the response of the basolateral amygdala to unconsciously processed fearful faces. *Neuron, 44*(6), 1043–1055.

Etkin, A., & Wager, T. D. (2007). Functional neuroimaging of anxiety: A meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. *American Journal of Psychiatry, 164*(10), 1476–1488.

Eysenck, H. J. (1976). The learning theory model of neurosis—A new approach. *Behavioral Research Theory, 14*(4), 251–267.

Eysenck, M. W., Derakshan, N., Santos, R., & Calvo, M. G. (2007). Anxiety and cognitive performance: Attentional control theory. *Emotion, 7*(2), 336–353.

Eysenck, M. W., MacLeod, C., & Mathews, A. (1987). Cognitive functioning and anxiety. *Psychological Research, 49*(2–3), 189–195.

Feigon, S. A., Waldman, I. D., Levy, F., & Hay, A. D. (2001). Genetic and environmental influences on separation anxiety disorder symptoms and their moderation by age and sex. *Behavior Genetics, 31,* 403–411.

Feldner, M. T., Zvolensky, M. J., Babson, K., Leen-Feldner, E. W., & Schmidt, N. B. (2008). An integrated approach to panic prevention targeting the empirically supported risk factors of smoking and anxiety sensitivity: Theoretical basis and evidence from a pilot project evaluating feasibility and short-term efficacy. *Journal of Anxiety Disorders, 22*(7), 1227–1243.

Feldner, M. T., Zvolensky, M. J., & Schmidt, N. B. (2004). Prevention of anxiety psychopathology: A critical review of the

___S
___E
___L

empirical literature. *Clinical Psychology: Science and Practice, 11*(4), 405–424.

Foa, E. B., Feske, U., Murdock, T. B., Kozak, M. J., & McCarthy, P. R. (1991). Processing of threat-related information in rape victims. *Journal of Abnormal Psychology, 100*(2), 156–162.

Foa, E. B., & Kozak, M. J. (1986). Emotional processing of fear: exposure to corrective information. *Psychological Bulletin, 99*(1), 20–35.

Foa, E. B., & McNally, R. J. (1986). Sensitivity to feared stimuli in obsessive-compulsives: A dichotic listening analysis. *Cognitive Therapy and Research, 10*, 477–486.

Ford, T., Goodman, R., & Meltzer, H. (2003). The British child and adolescent mental health survey 1999: The prevalence of DSM-IV disorders. *Journal of the American Academy of Child & Adolescent Psychiatry, 42,* 1203–1211.

Fox, E. (1993). Attentional bias in anxiety: Selective or not? *Behaviour Research and Therapy, 31*(5), 487–493.

Fox, E., Russo, R., Bowles, R., & Dutton, K. (2001). Do threatening stimuli draw or hold visual attention in subclinical anxiety? *Journal of Experimental Psychology: General, 130*(4), 681–700.

Freud, S. (1924). *A general introduction to psychoanalysis.* New York: Washington Square Press.

Fridlund, A. J., & Cacioppo, J. T. (1986). Guidelines for human electromyographic research. *Psychophysiology, 23*(5), 567–589.

Friedman, B. H., & Thayer, J. F. (1998). Anxiety and autonomic flexibility: A cardiovascular approach. *Biological Psychology, 49*(3), 303–323.

Friedman, B. H., Thayer, J. F., Borkovec, T. D., Tyrrell, R. A., Johnson, B. H., & Columbo, R. (1993). Autonomic characteristics of nonclinical panic and blood phobia. *Biological Psychiatry, 34*(5), 298–310.

Fyer, A. J., Mannuzza, S., Chapman, T. F., Liebowitz, M. R., & Klein, D. F. (1993). A direct interview family study of social phobia. *Archives of General Psychiatry, 50*(4), 286–293.

Geller, V., & Shaver, P. (1976). Cognitive consequences of self-awareness. *Journal of Experimental Social Psychology, 12*(99–108).

Giegling, I., Hartmann, A. M., Moller, H. J., & Rujescu, D. (2006). Anger- and aggression-related traits are associated with polymorphisms in the 5-HT-2A gene. *Journal of Affective Disorders, 96*(1–2), 75–81.

Goldin, P. R., McRae, K., Ramel, W., & Gross, J. J. (2008). The neural bases of emotion regulation: Reappraisal and suppression of negative emotion. *Biological Psychiatry, 63*(6), 577–586.

Goldstein, R. B., Wickramaratne, P. J., Horwath, E., & Weissman, M. M. (1997). Familial aggregation and phenomenology of 'early'-onset (at or before age 20 years) panic disorder. *Archives of General Psychiatry, 54,* 271–278.

Gonzalez-Bono, E., Moya-Albiol, L., Salvador, A., Carrillo, E., Ricarte, J., & Gomez-Amor, J. (2002). Anticipatory autonomic response to a public speaking task in women: The role of trait anxiety. *Biological Psychiatry, 60*(1), 37–49.

Goodyer, I. M., Wright, C., & Altham, P.M.E. (1989). Recent friendships in anxious and depressed school age children. *Psychological Medicine, 19,* 165–174.

Gorman, J. M., & Sloan, R. P. (2000). Heart rate variability in depressive and anxiety disorders. *American Heart Journal, 140*(4 Suppl.), 77–83.

Gorwood, P., Feingold, J., & Ades, J. (1999). Epidémiologie génétique et psychiatrie (I): Portées et limites des études de concentration familial—exemple du trouble panique. *L'Encephale, 10,* 21–29.

Gotlib, I. H., Kasch, K. L., Traill, S., Joormann, J., Arnow, B. A., & Johnson, S. L. (2004). Coherence and specificity of information-processing biases in depression and social phobia. *Journal of Abnormal Psychology, 113*(3), 386–398.

Gottesman, II, & Gould, T. D. (2003). The endophenotype concept in psychiatry: Etymology and strategic intentions. *American Journal of Psychiatry, 160*(4), 636–645.

Grachev, I. D., & Apkarian, A. V. (2000). Anxiety in healthy humans is associated with orbital frontal chemistry. *Molecular Psychiatry, 5*(5), 482–488.

Gray, J. A., & McNaughton, N. (2000). *The neuropsychology of anxiety: An enquiry into the functions of the septo-hippocampal system* (2nd ed.). New York: Oxford University Press.

Gregory, A. M., Caspi, A., Moffitt, T. E., Koenen, K., Eley, T. C., & Poulton, R. (2007). Juvenile mental health histories of adults with anxiety disorders. *American Journal of Psychiatry, 164,* 301–308.

Gregory, A. M., & Eley, T. C. (2007). Genetic influences on anxiety in children: What we've learned and where we're heading. *Clinical Child & Family Psychology Review, 10,* 199–212.

Gregory, A. M., Eley, T. C., & Plomin, R. (2004). Exploring the association between anxiety and conduct problems in a large sample of twins aged 2–4. *Journal of Abnormal Child Psychology, 33,* 111–122.

Grillon, C. (2002). Startle reactivity and anxiety disorders: Aversive conditioning, context, and neurobiology. *Biological Psychiatry, 52*(10), 958–975.

Grillon, C., Dierker, L., Merikangas, K. R. (1997). Startle modulation in children at risk for anxiety disorders and/or alcoholism. *Journal of the American Academy of Child & Adolescent Psychiatry, 36,* 925–932.

Grillon, C., Morgan, C. A., III, Davis, M., & Southwick, S. M. (1998a). Effect of darkness on acoustic startle in Vietnam veterans with PTSD. *American Journal of Psychiatry, 155*(6), 812–817.

Grillon, C., Morgan, C. A., III, Davis, M., & Southwick, S. M. (1998b). Effects of experimental context and explicit threat cues on acoustic startle in Vietnam veterans with posttraumatic stress disorder. *Biological Psychiatry, 44*(10), 1027–1036.

Gross, C., & Hen, R. (2004). The developmental origins of anxiety. *Nature Reviews Neuroscience, 5*(7), 545–552.

Gross, J. J. (1998). Antecedent- and response-focused emotion regulation: Divergent consequences for experience, expression, and physiology. *Journal of Personality and Social Psychology, 74*(1), 224–237.

Gross, J. J. (2002). Emotion regulation: Affective, cognitive, and social consequences. *Psychophysiology, 39*(3), 281–291.

Gunthert, K. C., Conner, T. S., Armeli, S., Tennen, H., Covault, J., & Kranzler, H. R. (2007). Serotonin transporter gene polymorphism (5-HTTLPR) and anxiety reactivity in daily life: A daily process approach to gene-environment interaction. *Psychosomatic Medicine, 69*(8), 762–768.

Gunther, T., Holtkamp, K., Jolles, J., Herpertz-Dahlmann, B., & Konrad, K. (2004). Verbal memory and aspects of attentional control in children and adolescents with anxiety disorders

or depressive disorders. *Journal of Affective Disorders, 82,* 265–269.

Gutknecht, L., Jacob, C., Strobel, A., Kriegebaum, C., Muller, J., Zeng, Y., et al. (2007). Tryptophan hydroxylase-2 gene variation influences personality traits and disorders related to emotional dysregulation. *International Journal of Neuropsychopharmacology, 10*(3), 309–320.

Hadwin, J. A., Donnelly, N., French, C. C., Richards, A., Watts, D., & Daley, D. (2003). The influences of children's self-report trait anxiety and depression on visual search for emotional faces. *Journal of Child Psychology and Psychiatry, 44*(3), 432—444.

Hadwin, J., Frost, S., French, C., & Richards, A. (1997). Cognitive processing and anxiety in typically developing children: Evidence for an interpretation bias. *Journal of Abnormal Psychology, 106,* 486–490.

Hamann, S., & Harenski, C. L. (2004). Exploring the brain's interface between personality, mood, and emotion: Theoretical comment on Canli et al. (2004). *Behavioral Neuroscience, 118*(5), 1134–1136.

Hariri, A. R., & Lewis, D. A. (2006). Genetics and the future of clinical psychiatry. *American Journal of Psychiatry, 163*(10), 1676–1678.

Hariri, A. R., Mattay, V. S., Tessitore, A., Kolachana, B., Fera, F., Goldman, D., et al. (2002). Serotonin transporter genetic variation and the response of the human amygdala. *Science, 297*(5580), 400–403.

Harmon-Jones, E. (2003). Early career award. Clarifying the emotive functions of asymmetrical frontal cortical activity. *Psychophysiology, 40*(6), 838–848.

Harrison, L. K., & Turpin, G. (2003). Implicit memory bias and trait anxiety: A psychophysiological analysis. *Biological Psychiatry, 62*(2), 97–114.

Harvey, A. G., & Bryant, R. A. (1998). The relationship between acute stress disorder and posttraumatic stress disorder: A prospective evaluation of motor vehicle accident survivors. *Journal of Consulting and Clinical Psychology, 66*(3), 507–512.

Hayward, C., Killen, J. D., Kraemer, H. C., & Taylor, C. B. (2000). Predictors of panic attacks in adolescents. *Journal of the American Academy of Child & Adolescent Psychiatry, 39,* 207–214.

Hegel, M. T., & Ferguson, R. J. (1997). Psychophysiological assessment of respiratory function in panic disorder: Evidence for a hyperventilation subtype. *Psychosomatic Medicine, 59*(3), 224–230.

Heils, A., Teufel, A., Petri, S., Stober, G., Riederer, P., Bengel, D., et al. (1996). Allelic variation of human serotonin transporter gene expression. *Journal of Neurochemistry, 66*(6), 2621–2624.

Heim-Dreger, U., Kohlmann, C., Eschenbeck, H., & Burkhardt, U. (2006). Attentional biases for threatening faces in children: Vigilant and avoidant processes. *Emotion, 6,* 320–325.

Heinz, A., Smolka, M. N., Braus, D. F., Wrase, J., Beck, A., Flor, H., et al. (2007). Serotonin transporter genotype (5-HTTLPR): Effects of neutral and undefined conditions on amygdala activation. *Biological Psychiatry, 61*(8), 1011–1014.

Heller, W. (1993). Neuropsychological mechanisms of individual differences in emotion, personality, and arousal. *Neuropsychology, 7,* 476–489.

Heller, W., Nitschke, J. B., Etienne, M. A., & Miller, G. A. (1997). Patterns of regional brain activity differentiate types of anxiety. *Journal of Abnormal Psychology, 106*(3), 376–385.

Herrmann, M. J., Huter, T., Muller, F., Muhlberger, A., Pauli, P., Reif, A., et al. (2007). Additive effects of serotonin transporter and tryptophan hydroxylase-2 gene variation on emotional processing. *Cerebral Cortex, 17*(5), 1160–1163.

Hirshfeld, D. R., Rosenbaum, J. F., Biederman, J., Bolduc, E. A., Faraone, S. V., Snidman N., et al. (1992). Stable behavioral inhibition and its association with anxiety disorder. *Journal of the American Academy of Child & Adolescent Psychiatry, 31,* 103–111.

Hofmann, S. G., Newman, M. G., Ehlers, A., & Roth, W. T. (1995). Psychophysiological differences between subgroups of social phobia. *Journal of Abnormal Psychology, 104*(1), 224–231.

Hope, D. A., Rapee, R. M., Heimberg, R. G., & Dombeck, M. J. (1990). Representations of the self in social phobia: Vulnerability to social threat. *Cognitive Therapy and Research, 14,* 477–485.

Hranilovic, D., Stefulj, J., Schwab, S., Borrmann-Hassenbach, M., Albus, M., Jernej, B., et al. (2004). Serotonin transporter promoter and intron 2 polymorphisms: Relationship between allelic variants and gene expression. *Biological Psychiatry, 55*(11), 1090–1094.

Hu, X. Z., Lipsky, R. H., Zhu, G., Akhtar, L. A., Taubman, J., Greenberg, B. D., et al. (2006). Serotonin transporter promoter gain-of-function genotypes are linked to obsessive-compulsive disorder. *American Journal of Human Genetics, 78*(5), 815–826.

Hudziak, J. J., Copeland, W., Stanger, C., & Wadsworth, M. (2004). Screening for DSM-IV externalizing disorders with the Child Behavior Checklist: A receiver-operating characteristic analysis. *Journal of Child Psychology and Psychiatry, 45,* 1299–1307

Hunnerkopf, R., Strobel, A., Gutknecht, L., Brocke, B., & Lesch, K. P. (2007). Interaction between BDNF Val66Met and dopamine transporter gene variation influences anxiety-related traits. *Neuropsychopharmacology, 32*(12), 2552–2560.

James, G. D., Yee, L. S., Harshfield, G. A., Blank, S. G., & Pickering, T. G. (1986). The influence of happiness, anger, and anxiety on the blood pressure of borderline hypertensives. *Psychosomatic Medicine, 48*(7), 502–508.

Jennings, J. R., Berg, W. K., Hutcheson, J. S., Obrist, P., Porges, S., & Turpin, G. (1981). Publication Guidelines for Heart Rate Studies in Man. *Psychophysiology, 18*(3), 226–231.

Johnson, J. G., Cohen, P., Pine, D. S., Klein, D. F., Kasen, S., & Brook, J. S. (2000). Association between cigarette smoking and anxiety disorders during adolescence and early adulthood. *Journal of the American Medical Association, 284*(18), 2348–2351.

Joiner, T. E., Catanzaro, S. J., & Laurent, J. (1996). Tripartite structure of positive and negative affect, depression, and anxiety in child and adolescent psychiatric inpatients. *Journal of Abnormal Psychology, 105,* 401–409.

Kagan, J. (1994). Galen's prophecy. New York: Basic Books.

Kagan J. (1995). On attachment. *Harvard Review of Psychiatry, 3,* 104–106.

Kagan, J., Reznick, J. S., & Snidman, N. (1987). The physiology and psychology of behavioral inhibition in children. *Child Development, 58,* 1459–1473.

Kagan, J., Snidman, N., Zentner. M., & Peterson, E. (1999). Infant temperament and anxious symptoms in school age children. *Development and Psychopathology, 11,* 209–224.

Kahneman, D., & Tversky, A. (1984). Choices, values and frames. *American Psychologist, 39,* 341–350.

Kashani, J. H., & Orvaschel, H. (1990). A community study of anxiety in children and adolescents. *American Journal of Psychiatry, 147,* 313–318.

Keltner, D., & Gross, J. J. (1999). Functional accounts of emotions. *Cognition and Emotion, 13*(5), 467–480.

Kendall, P. C., & Ronan, K. R. (1990). Assessment of children's anxieties, fears, and phobias: Cognitive behavioral models and methods. In C. R. Reynolds & R. W. Kamphaus (Eds.), *Handbook of psychological and educational assessment of children.* New York: Guilford Press.

Kendall, P. C., & Warman, M. J. (1996). Anxiety disorders in youth: Diagnostic consistency across DSM-III-R and DSM-IV. *Journal of Anxiety Disorders, 10,* 453–463.

Kendler, K. S., Neale, M. C., Kessler, R. C., Heath, A. C., & Eaves, L. J. (1992a). The genetic epidemiology of phobias in women. The interrelationship of agoraphobia, social phobia, situational phobia, and simple phobia. *Archives of General Psychiatry, 49*(4), 273–281.

Kendler, K. S., Neale, M. C., Kessler, R. C., Heath, A. C., Eaves, L. J. (1992b). Major depression and generalized anxiety disorder: Same genes, (partly) different environments? *Archives of General Psychiatry, 49,* 716–722.

Kendler, K. S., Neale, M. C., Kessler, R. C., Heath, A. C., & Eaves, L. J. (1993). The lifetime history of major depression in women: Reliability of diagnosis and heritability. *Archives of General Psychiatry, 50,* 863–870.

Kendler, K. S., Walters, E. E., Neale, M. C., Kessler, R. C., Heath, A. C., & Eaves, L. J. (1995). The structure of the genetic and environmental risk factors for six major psychiatric disorders in women: Phobia, generalized anxiety disorder, panic disorder, bulimia, major depression, and alcoholism. *Archives of General Psychiatry, 52*(5), 374–383.

Kessler, R. C. (2007). The global burden of anxiety and mood disorders: Putting the European Study of the Epidemiology of Mental Disorders (ESEMeD) findings into perspective. *Journal of Clinical Psychiatry, 68*(Suppl. 2), 10–19.

Kessler, R. C., Berglund, P., Demler, O., Jin, R., & Walters, E. E. (2005). Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the national comorbidity survey replication. *Archives of General Psychiatry, 62,* 593–602.

Kessler, R. C., Chiu, W. T., Demler, O., Merikangas, K. R., & Walters, E. E. (2005). Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry, 62*(6), 617–627.

Kessler, R. C., McGonagle, K. A., Zhao, S., Nelson, C. B., Hughes, M., Eshleman, S., et al. (1994). Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States: results from the National Comorbidity Survey. *Archives of General Psychiatry, 51,* 8–19.

Kindt, M., & Brosschot, J. F. (1997). Phobia-related cognitive bias for pictorial and linguistic stimuli. *Journal of Abnormal Psychology, 106*(4), 644–648.

Kindt, M., Brosschot, J. F., & Everaerd, W.T.A.M. (1997). Cognitive bias in children in a real life stress situation and a neutral situation. *Journal of Experimental Child Psychology, 64,* 79–94.

King, N. J., Ollendick, T. H., & Gullone, E. (1991). Negative affectivity in children and adolescents: Relations between anxiety and depression. *Clinical Psychology Review, 11,* 441–459.

Kingwell, B. A., Thompson, J. M., Kaye, D. M., McPherson, G. A., Jennings, G. L., & Esler, M. D. (1994). Heart rate spectral analysis, cardiac norepinephrine spillover, and muscle sympathetic nerve activity during human sympathetic nervous activation and failure. *Circulation, 90*(1), 234–240.

Klein, E., Cnaani, E., Harel, T., Braun, S., & Ben-Haim, S. A. (1995). Altered heart rate variability in panic disorder patients. *Biological Psychiatry, 37*(1), 18–24.

Koster, E. H., Crombez, G., Van Damme, S., Verschuere, B., & de Houwer, J. (2004). Does imminent threat capture and hold attention? *Emotion, 4*(3), 312–317.

Kovacs, M., Gatsonis, C., Paulaskas, S. L., & Richards, C. (1989). Depressive disorders in childhood. *Archives of General Psychiatry, 46,* 776–782.

Kowalski, R. M. (2000). Anxiety. In A. E. Kazdin (Ed.), *Encyclopedia of psychology.* Washington, DC: American Psychological Association.

Krain, A. L., Gotimer, K., Hefton, S., Ernst, M., Castellanos, F. X., Pine, D. S., et al. (2008). A functional magnetic resonance imaging investigation of uncertainty in adolescents with anxiety disorders. *Biological Psychiatry, 63*(6), 563–568.

Kroes, M., Kalff, A. C., Kessel, A., Steyaert, J., Feron, F., Van Someren, A., et al. (2001). Child psychiatric diagnoses in a population of Dutch schoolchildren aged 6–8 years. *Journal of the American Academy of Child & Adolescent Psychiatry, 40,* 1401–1409.

Krohne, H. W., & Hock, M. (1991). Relationships between restrictive mother-child interactions and anxiety of the child. *Anxiety Research, 4*(2), 109–124.

Ladouceur, C. D., Dahl, R. E, Williamson, D. E., Birmaher, B., Ryan, N. D., & Casey, B. J. (2005). Altered emotional processing in pediatric anxiety, depression, and comorbid anxiety-depression. *Journal of Abnormal Child Psychology, 33,* 165–177.

Lakatos, K., Nemoda, Z., Birkas, E., Ronai, Z., Kovacs, E., Ney, K., et al. (2003). Association of D4 dopamine receptor gene and serotonin transporter promoter polymorphisms with infants' response to novelty. *Molecular Psychiatry, 8,* 90–97.

Landis, C., & Hunt, W. A. (1939). *The startle pattern.* New York: Farrar and Rinehart.

Lang, P. J. (1995). The emotion probe. Studies of motivation and attention. *American Psychologist, 50*(5), 372–385.

Lang, P. J., Bradley, M. M., & Cuthbert, B. N. (1990). Emotion, attention, and the startle reflex. *Psychological Review, 97*(3), 377–395.

Larson, C. L., Davidson, R. J., Abercrombie, H. C., Ward, R. T., Schaefer, S. M., Jackson, D.C., et al. (1998). Relations between PET-derived measures of thalamic glucose metabolism and EEG alpha power. *Psychophysiology, 35*(2), 162–169.

Last, C. G., Perrin, S., Hersen, M., & Kazdin, A. E. (1992). DSM-III-R anxiety disorders in children: Sociodemographic and clinical characteristics. *Journal of the American Academy of Child and Adolescent Psychiatry, 31,* 1070–1076.

Last, C. G., Perrin, S., Hersen, M., & Kazdin, A. E. (1996). A prospective study of child anxiety disorders. *Journal of*

AuQ3

S___
E___
L___

the American Academy of Child & Adolescent Psychiatry, 35, 1502–1510.

Lau, J. Y., Eley, T. C., & Stevenson, J. (2006). Examining the state-trait anxiety relationship: A behavioural genetic approach. *Journal of Abnormal Psychology, 34*(1), 19–27.

Lauriola, M., & Levin, I. P. (2001). Personality traits and risky decision-making in a controlled experimental task: An exploratory study. *Personality and Individual Differences, 31,* 215–226.

Lazarus, R. S. (1982). Thoughts on the relation between emotion and cognition. *American Psychologist, 37*(9), 1019–1024.

Lazarus, R. S. (1993). From psychological stress to the emotions: A history of changing outlooks. *Annual Review of Psychology, 44,* 1–21.

LeDoux, J. E. (2000). Emotion circuits in the brain. *Annual Review of Neuroscience, 23,* 155–184.

Legrand, L. N., McGue, M., & Iacono, W. G. (2000). Early adolescent substance use: A search for gene-environment interactions and an understanding of the contributions of personality. *Behavior Genetics,* 29, 433–444.

Lenane, M. C., Swedo, S. E., Leonard, H., Pauls, D. L., Sceery, W., & Rapoport, J. L. (1990). Psychiatric disorders in first degree relatives of children and adolescents with obsessive compulsive disorder. *Journal of the American Academy of Child & Adolescent Psychiatry, 29,* 407–412.

Lesch, K. P., Bengel, D., Heils, A., Sabol, S. Z., Greenberg, B. D., Petri, S., et al. (1996). Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. *Science, 274*(5292), 1527–1531.

Lesch, K. P., Wolozin, B. L., Murphy, D. L., & Reiderer, P. (1993). Primary structure of the human platelet serotonin uptake site: Identity with the brain serotonin transporter. *Journal of Neurochemistry, 60*(6), 2319–2322.

Lewinsohn, P., Zinbarg, R., Seeley, J., Lewinsohn, M., & Sack, W. (1997). Comorbidity between anxiety disorders and between anxiety disorders and other mental disorders in children. *Journal of Anxiety Disorders, 11,* 377–394.

Lewis, L. E., & Drewett, R. F. (2006). Psychophysiological correlates of anxiety: A single-case study. *Journal of Anxiety Disorders, 20*(6), 829–835.

Lichtenstein, P., & Annas, P. (1997). The heritability of specific fears and phobias in children. *Behavior Genetics, 27,* 598.

Lichtenstein, P., & Annas, P. (2000). Heritability and prevalence of specific fears and phobias in childhood. *Journal of Child Psychology and Psychiatry, 41,* 927–937.

Lilienfeld, S. O., Turner, S. M., & Jacob, R. G. (1998). Déjà vu all over again: Critical misunderstandings concerning anxiety sensitivity and constructive suggestions for future research. *Journal of Anxiety Disorders, 12,* 71–82.

Lindauer, R. T., van Meijel, E. P., Jalink, M., Olff, M., Carlier, I. V., & Gersons, B. P. (2006). Heart rate responsivity to script-driven imagery in posttraumatic stress disorder: Specificity of response and effects of psychotherapy. *Psychosomatic Medicine, 68*(1), 33–40.

Lonigan, C. J., Carey, M. P., & Finch, A. J., Jr. (1994). Anxiety and depression in children and adolescents: Negative affectivity and the utility of self-reports. *Journal of Consulting and Clinical Psychology, 62,* 1000–1008.

Lonigan, C. J., Hooe, E. S., David, C. F., & Kistner, J. A. (1999). Positive and negative affectivity in children: Confirmatory factor analysis of a two-factor model and its relation to symptoms of anxiety and depression. *Journal of Consulting and Clinical Psychology, 67, 374–386.*

Lonigan, C. J., & Phillips, B. M. (2001). Temperamental basis of anxiety disorders in children. In M. W. Vasey & M. R. Dadds (Eds.), *The developmental psychopathology of anxiety* (pp. 60–91). New York: Oxford University Press.

Lonigan, C. J., Vasey, M. W., Phillips, B. M., & Hazen, R. A. (2004). Temperament, anxiety, and the processing of threat-relevant stimuli. *Journal of Clinical Child and Adolescent Psychology, 33*(1), 8–20.

Lotta, T., Vidgren, J., Tilgmann, C., Ulmanen, I., Melen, K., Julkunen, I., et al. (1995). Kinetics of human soluble and membrane-bound catechol O-methyltransferase: A revised mechanism and description of the thermolabile variant of the enzyme. *Biochemistry, 34*(13), 4202–4210.

MacLeod, C. (1990). Mood disorders and cognition. In M. W. Eysenck (Ed.), *Cognitive psychology: An international review* (pp. 9–55). New York: Wiley.

MacLeod, C. (2008). *Attentional bias modification in anxiety.* Paper presented at the 29th Stress and Anxiety Research Conference. Retrieved August 11, 2009, from http://www.bbk.ac.uk/psyc/star/finalprogramme

MacLeod, C., & Hagan, R. (1992). Individual differences in the selective processing of threatening information, and emotional responses to a stressful life event. *Behaviour Research and Therapy, 30*(2), 151–161.

MacLeod, C., Mathews, A., & Tata, P. (1986). Attentional bias in emotional disorders. *Journal of Abnormal Psychology, 95*(1), 15–20.

MacLeod, C., & Rutherford, E. M. (1992). Anxiety and the selective processing of emotional information: Mediating roles of awareness, trait and state variables, and personal relevance of stimulus materials. *Behaviour Research and Therapy, 30*(5), 479–491.

MacLeod, C., Rutherford, E., Campbell, L., Ebsworthy, G., & Holker, L. (2002). Selective attention and emotional vulnerability: Assessing the causal basis of their association through the experimental manipulation of attentional bias. *Journal of Abnormal Psychology, 111,* 107–123.

Magnusdottir, I., & Smari, J. (1999). Social anxiety in adolescents and appraisal of negative events: Specificity or generality of bias? *Behavioural and Cognitive Psychotherapy, 27,* 223–230.

Malik, M., Bigger, J. T., Camm, A. J., Kleiger, R. E., Malliani, A., Moss, A. J., et al. (1996). Heart rate variability: Standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Circulation, 93*(5), 1043–1065.

Maner, J. K., Richey, J. A., Cromer, K., Mallott, M., Lejuez, C. W., Joiner, T. E., et al. (2007). Dispositional anxiety and risk-avoidant decision-making. *Personality and Individual Differences, 42,* 665–675.

Martin, M., Horder, P., & Jones, G. V. (1992). Integral bias in naming phobia-related words. *Cognition and Emotion, 6,* 479–486.

Martin, M., & Jones, G. V. (1995). Integral bias in the cognitive processing of emotionally linked pictures. *British Journal of Psychology, 86,* 419–435.

Mathersul, D., Williams, L. M., Hopkinson, P. J., & Kemp, A. H. (2008). Investigating models of affect: Relationships among EEG alpha asymmetry, depression, and anxiety. *Emotion, 8*(4), 560–572.

Mathews, A. (1990). Why worry? The cognitive function of anxiety. *Behaviour Research and Therapy, 28*(6), 455–468.

Mathews, A., Fox, E., Yiend, J., & Calder, A. (2003). The face of fear: Effects of eye gaze and emotion on visual attention. *Visual Cognition, 10*(7), 823–835.

Mathews, A., Mackintosh, B., & Fulcher, E. P. (1997). Cognitive biases in anxiety and attention to threat. *Trends in Cognitive Sciences, 1,* 340–345.

Mathews, A., & MacLeod, C. (1985). Selective processing of threat cues in anxiety states. *Behaviour Research and Therapy, 23*(5), 563–569.

Mathews, A., & MacLeod, C. (1986). Discrimination of threat cues without awareness in anxiety states. *Journal of Abnormal Psychology, 95*(2), 131–138.

Mathews, A., & MacLeod, C. (1994). Cognitive approaches to emotion and emotional disorders. *Annual Review of Psychology, 45,* 25–50.

Mathews, A., & MacLeod, C. (2002). Induced processing biases have causal effects on anxiety. *Cognition and Emotion, 16,* 331–354.

Mathews, A., & MacLeod, C. (2005). Cognitive vulnerability to emotional disorders. *Annual Review of Clinical Psychology, 1,* 167–195.

Mathews, A., May, J., Mogg, K., & Eysenck, M. (1990). Attentional bias in anxiety: Selective search or defective filtering? *Journal of Abnormal Psychology, 99*(2), 166–173.

Mathews, A., Mogg, K., Kentish, J., & Eysenck, M. (1995). Effect of psychological treatment on cognitive bias in generalized anxiety disorder. *Behaviour Research and Therapy, 33*(3), 293–303.

Mathews, A., Mogg, K., May, J., & Eysenck, M. (1989). Implicit and explicit memory bias in anxiety. *Journal of Abnormal Psychology, 98*(3), 236–240.

Mathews, A., Richards, A., & Eysenck, M. (1989). Interpretation of homophones related to threat in anxiety states. *Journal of Abnormal Psychology, 98*(1), 31–34.

Mathews, A., Ridgeway, V., Cook, E., & Yiend, J. (2007). Inducing a benign interpretational bias reduces trait anxiety. *Journal of Behavioral Therapy and Experimental Psychiatry, 38*(2), 225–236.

Mauss, I. B., Wilhelm, F. H., & Gross, J. J. (2003). Autonomic recovery and habituation in social anxiety. *Psychophysiology, 40*(4), 648–653.

McClure, E. B., Adler, A., Monk, C. S., Cameron, J., Smith, S., Nelson, E. E., et al. (2007). fMRI predictors of treatment outcome in pediatric anxiety disorders. *Psychopharmacology, 191,* 97–105.

McNally, R. J. (1995). Automaticity and the anxiety disorders. *Behaviour Research and Therapy, 33*(7), 747–754.

McNally, R. J. (1996). Anxiety sensitivity is distinguishable from trait anxiety. In R. M. Rapee (Ed.), *Current controversies in anxiety disorder research.* New York: Guilford Press.

McNally, R. J., Kaspi, S. P., Riemann, B. C., & Zeitlin, S. B. (1990). Selective processing of threat cues in posttraumatic stress disorder. *Journal of Abnormal Psychology, 99*(4), 398–402.

McNally, R. J., Metzger, L. J., Lasko, N. B., Clancy, S. A., & Pitman, R. K. (1998). Directed forgetting of trauma cues in adult survivors of childhood sexual abuse with and without posttraumatic stress disorder. *Journal of Abnormal Psychology,, 107*(4), 596–601.

McNally, R. J., Riemann, B. C., & Kim, E. (1990). Selective processing of threat cues in panic disorder. *Behaviour Research and Therapy, 28*(5), 407–412.

McNally, R. J., Riemann, B. C., Louro, C. E., Lukach, B. M., & Kim, E. (1992). Cognitive processing of emotional information in panic disorder. *Behavioral Research Theory, 30*(2), 143–149.

Melchior, M., Caspi, A., Milne, B. J., Danese, A., Poulton, R., & Moffitt, T. E. (2007). Work stress precipitates depression and anxiety in young, working women and men. *Psychological Medicine, 37*(8), 1119–1129.

Melzig, C. A., Weike, A. I., Hamm, A. O., & Thayer, J. F. (2008). Individual differences in fear-potentiated startle as a function of resting heart rate variability: Implications for panic disorder. *International Journal of Psychophysiology.*

Merikangas, K., Avenevoli, S., Dierker, L., & Grillon, C. (1999). Vulnerability factors among children at risk for anxiety disorders. *Biological Psychiatry, 46,* 1523–1535.

Merikangas, K., & Pine, D. (2002). Genetic and other vulnerability factors for anxiety and stress disorders. In K.L. Davis, D. Charney, J.T. Coyle, & C. Nemeroff (Eds.), *Neuropsychopharmacology: The fifth generation of progress* (pp. 868–882). Philadelphia: Lippincott Williams & Wilkins.

Merikangas, K., & Pine, D. (2008). Vulnerability for anxiety and other stress-related disorders. In D. Charney & E. Nestler (Eds.), *Neurobiology of mental illness* (pp. 867–882). New York: Oxford University Press.

Metzger, L. J., Paige, S. R., Carson, M. A., Lasko, N. B., Paulus, L. A., Pitman, R. K., et al. (2004). PTSD arousal and depression symptoms associated with increased right-sided parietal EEG asymmetry. *Journal of Abnormal Psychology, 113*(2), 324–329.

Miech, R. A., Caspi, A., Moffitt, T. E., Wright, B.R.E., & Silva, P. A. (1999). Low socioeconomic status and mental disorders: A longitudinal study of selection and causation during young adulthood. *American Journal of Sociology, 104,* 1096–1131.

Millham, M. P., Nugent, A. C., Drevets, W. C., Leibenluft, E., Ernst, M., Charney, D.S., & Pine, D.S. (2005). Selective reduction in amygdala volume in pediatric generalized anxiety disorder: A voxel-based morphometry investigation. *Biological Psychiatry, 57,* 961–966.

Mineka, S., Gunnar, M., & Champoux, M. (1986). Control and early socio-emotional development: Infant rhesus monkeys reared in controllable versus uncontrollable environments. *Child Development, 57,* 1241–1256.

Mineka, S., & Zinbarg, R. (2006). A contemporary learning theory perspective on the etiology of anxiety disorders: It's not what you thought it was. *American Psychology, 61*(1), 10–26.

Miu, A. C. (2008). Genetic contributions to individual differences in emotion: A primer. *Reviews in the Neurosciences, 19*(6), 467–474.

Miu, A. C., Heilman, R. M., & Houser, D. (2008). Anxiety impairs decision-making: Psychophysiological evidence from an Iowa Gambling Task. *Biological Psychology, 77*(3), 353–358.

AuQ4

S___
E___
L___

Miu, A. C., Heilman, R. M., & Miclea, M. (2009). Reduced heart rate variability and vagal tone in anxiety: Trait versus state, and the effects of autogenic training. *Autonomic Neuroscience, 145*(1–2), 99–103.

Miu, A. C., Heilman, R. M., Opre, A., & Miclea, M. (2005). Emotion-induced retrograde amnesia and trait anxiety. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 31*(6), 1250–1257.

Miu, A. C., Miclea, M., & Houser, D. (2008). Anxiety and decision-making: Toward a neuroeconomics perspective. In D. Houser & K. McCabe (Eds.), *Neuroeconomics* (pp. 55–84). London: Emerald Insight.

Mogg, K., Baldwin, D. S., Brodrick, P., & Bradley, B. P. (2004). Effect of short-term SSRI treatment on cognitive bias in generalised anxiety disorder. *Psychopharmacology, 176*(3–4), 466–470.

Mogg, K., & Bradley, B. P. (1999). Orienting of attention to threatening facial expressions presented under conditions of restricted awareness. *Cognition and Emotion, 13*(6), 713–740.

Mogg, K., Bradley, B. P., Dixon, C., Fisher, S., Twelftree, H., & McWilliams, A. (2000). Trait anxiety, defensiveness and selective processing of threat: An investigation using two measures of attentional bias. *Personality and Individual Differences, 28,* 1063–1077.

Mogg, K., Bradley, B. P., Millar, N., & White, J. (1995). A follow-up study of cognitive bias in generalized anxiety disorder. *Behaviour Research and Therapy, 33*(8), 927–935.

Mogg, K., Bradley, B. P., Williams, R., & Mathews, A. (1993). Subliminal processing of emotional information in anxiety and depression. *Journal of Abnormal Psychology, 102*(2), 304–311.

Mogg, K., Mathews, A., Bird, C., & MacGregor-Morris, R. (1990). Effects of stress and anxiety on the processing of threat stimuli. *Journal of Personality and Social Psychology, 59,* 1230–1237.

Mogg, K., Mathews, A., & Weinman, J. (1987). Memory bias in clinical anxiety. *Journal of Abnormal Psychology, 96*(2), 94–98.

Monk, C. S., Nelson, E. E., McClure, E. B., Mogg, K., Bradley, B.P., Leibenluft, E., et al. (2006). Ventrolateral prefrontal cortex activation and attentional bias in response to angry faces in adolescents with generalized anxiety disorder. *American Journal of Psychiatry, 163,* 1091–1097.

Monk, C. S., Nelson, E. E., Woldehawariat, G., Montgomery, L., Zarahn, E., McClure, E., et al. (2004). Experience-dependent plasticity for attention to threat: Behavioral and neurophysiological evidence in humans. *Biological Psychiatry, 56,* 607–610.

Moradi, A. R., Taghavi, M. R., Neshat Doost, H. T., Yule, W., & Dalgleish, T. (1999). Performance of children and adolescents with PTSD on the Stroop colour-naming task. *Psychological Medicine, 29,* 415–419.

Morinaga, K., Akiyoshi, J., Matsushita, H., Ichioka, S., Tanaka, Y., Tsuru, J., et al. (2007). Anticipatory anxiety-induced changes in human lateral prefrontal cortex activity. *Biological Psychiatry, 74*(1), 34–38.

Mujica-Parodi, L. R., Korgaonkar, M., Ravindranath, B., Greenberg, T., Tomasi, D., Wagshul, M., et al. (2009). Limbic dysregulation is associated with lowered heart rate variability and increased trait anxiety in healthy adults. *Human Brain Mapping, 30*(1), 47–58.

Muris, P., Kindt, M., Bögels, S., Merckelbach, H., Gadet, B., & Moulaert, V. (2000). Anxiety and threat perception abnormalities in normal children. *Journal of Psychopathology and Behavioral Assessment, 22,* 183–199.

Muris, P., & Ollendick, T. H. (2005). The role of temperament in the etiology of child psychopathology. *Clinical Child and Family Psychology Review, 8,* 271–289.

Nesse, R. M. (1999). Proximate and evolutionary studies of stress and depression. *Neuroscience and Biobehavioral Reviews, 23,* 895–903.

Nielsen, D. A., Dean, M., & Goldman, D. (1992). Genetic mapping of the human tryptophan hydroxylase gene on chromosome 11, using an intronic conformational polymorphism. *American Journal of Human Genetics, 51*(6), 1366–1371.

Nugent, K., & Mineka, S. (1994). The effect of high and low trait anxiety on implicit and explicit tasks. *Cognition and Emotion, 8,* 147–163.

Nunn, J. D., Stevenson, R. J., & Whalan, G. (1984). Selective memory effects in agoraphobic patients. *British Journal of Clinical Psychology, 23*(Pt. 3), 195–201.

Ogilvie, A. D., Battersby, S., Bubb, V. J., Fink, G., Harmar, A. J., Goodwim, G. M., et al. (1996). Polymorphism in serotonin transporter gene associated with susceptibility to major depression. *Lancet, 347*(9003), 731–733.

Oldenburg, C., Lundh, L. G., & Kivistö, P. (2002). Explicit and implicit memory, trait anxiety, and repressive coping style. *Personality and Individual Differences, 32,* 107–119.

Owens, M., Stevenson, J., Norgate, R., & Hadwin, J. A. (2008). Working memory partially mediates the relationship between trait anxiety and academic performance. *Anxiety, Stress, & Coping, 21,* 417–430.

Paulus, M. P. (2007). Decision-making dysfunctions in psychiatry—altered homeostatic processing? *Science, 318*(5850), 602–606.

Pennington, B. F. (2002). The development of psychopathology: Nature and nurture. New York: Guilford Press.

Pérez-Edgar, K., & Fox, N. A. (2005). A behavioral and electrophysiological study of children's selective attention under neutral and affective conditions *Journal of Cognition & Development, 6,* 89–116.

Petruzzello, S. J., & Landers, D. M. (1994). State anxiety reduction and exercise: Does hemispheric activation reflect such changes? *Medicine and Science in Sports and Exercise, 26*(8), 1028–1035.

Pezawas, L., Meyer-Lindenberg, A., Drabant, E. M., Verchinski, B. A., Munoz, K. E., Kolachana, B. S., et al. (2005). 5-HTTLPR polymorphism impacts human cingulate-amygdala interactions: A genetic susceptibility mechanism for depression. *Nature Neuroscience, 8*(6), 828–834.

Picton, T. W., Bentin, S., Berg, P., Donchin, E., Hillyard, S. A., Johnson, R., et al. (2000). Guidelines for using human event-related potentials to study cognition: Recording standards and publication criteria. *Psychophysiology, 37*(2), 127–152.

Pine, D. S. (2007). Research review: A neuroscience framework for pediatric anxiety disorders. *Journal of Child Psychology and Psychiatry, 48,* 631–648.

Pine, D. S., Cohen, P., Gurley, D., Brook, J., & Ma, Y. (1998). The risk for early adulthood anxiety and depressive disorders in adolescents with anxiety and depressive disorders. *Archives of General Psychiatry, 55,* 56–64.

Pine, D. S., Klein, R. G., Coplan, J. D., Papp, L. A., Hoven, C. W., Martinez, J., et al. (2000). Differential carbon dioxide sensitivity in childhood anxiety disorders and non-ill comparison group. *Archives of General Psychiatry, 57,* 960–967.

Pine, D. S., Wasserman, G. A., & Workman, S. B. (1999). Memory and anxiety in prepubertal boys at risk for delinquency. *Journal of the American Academy of Child & Adolescent Psychiatry, 38,* 1024–1031.

Pine, D. S., Lissek, S., Klein, R. G., Mannuzza, S., Moulton, J. L. III, Guardino, M., & Woldehawariat, G. (2004). Face-memory and emotion: Associations with major depression in children and adolescents. *Journal of Child Psychology and Psychiatry, 45,* 1199–1208.

Pine, D. S., Klein, R. G., Roberson-Nay, R., Mannuzza, S., Moulton, J. L., III, Woldehawariat, G., & Guardino, M. (2005). Response to 5% carbon dioxide in children and adolescents: Relationship to panic disorder in parents and anxiety disorders in subjects. *Archives of General Psychiatry, 62,* 73–80.

Pivik, R. T., Broughton, R. J., Coppola, R., Davidson, R. J., Fox, N., & Nuwer, M. R. (1993). Guidelines for the recording and quantitative analysis of electroencephalographic activity in research contexts. *Psychophysiology, 30*(6), 547–558.

Plomin, R., DeFries, J. C., McClearn, G. E., & McGuffin, P. (2000). *Behavioral genetics* (4th ed.).New York: Worth.

Pole, N. (2007). The psychophysiology of posttraumatic stress disorder: A meta-analysis. *Psychological Bulletin, 133*(5), 725–746.

Pollock, R. A., Carter, A. S., Dierker, L., Chazan-Cohen, R., & Merikangas, K. R. (2002). Anxiety sensitivity in adolescents at risk for psychopathology. *Journal of Child Clinical Psychology, 31,* 343–353.

Prior, M., Smart, D., Sanson, A., & Oberklaid, F. (2000). Does shy-inhibited temperament in childhood lead to anxiety problems in adolescence? *Adolescence, 39,* 461–468.

Pynoos, R. S., Steinberg, A. M., & Piacentini, J. C. (1999). A developmental psychopathology model of childhood traumatic stress and intersection with anxiety disorders. *Biological Psychiatry, 46,* 1542–1554.

Rachman, S. (1977). The conditioning theory of fear-acquisition: A critical examination. *Behaviour Research and Therapy, 15*(5), 375–387.

Rahman, S., Sahakian, B. J., Cardinal, R. N., Rogers, R. D., & Robbins, T. W. (2001). Decision making and neuropsychiatry. *Trends in Cognitive Science, 5*(6), 271–277.

Ramamoorthy, S., Bauman, A. L., Moore, K. R., Han, H., Yang-Feng, T., Chang, A. S., et al. (1993). Antidepressant- and cocaine-sensitive human serotonin transporter: Molecular cloning, expression, and chromosomal localization. *Proceedings of the National Academy of Science, 90*(6), 2542–2546.

Rapee, R. M., & Heimberg, R. G. (1997). A cognitive-behavioral model of anxiety in social phobia. *Behaviour Research and Therapy, 35*(8), 741–756.

Reidy, J. (2004). Trait anxiety, trait depression, worry, and memory. *Behavioral Research Theory, 42*(8), 937–948.

Reidy, J., & Richards, A. (1997). Anxiety and memory: A recall bias for threatening words in high anxiety. *Behaviour Research and Therapy, 35*(6), 531–542.

Reidy, J., & Richards, A. (1997). A memory bias for threat in high-trait anxiety. *Personality and Individual Differences, 23,* 653–663.

Reiss, S. (1980). Pavlovian conditioning and human fear: An expectancy model. *Behavior Therapy, 11,* 380–396.

Reiss, S. (1997). Trait anxiety: It's not what you think it is. *Journal of Anxiety Disorders, 12,* 201–214.

Richards, A., & French, C. C. (1991). Effects of encoding and anxiety on implicit and explicit memory performance. *Personality and Individual Differences, 12,* 131–139.

Richards, J. C., Austin, D. A., & Alvarenga, M. E. (2001). Interpretation of ambiguous interoceptive stimuli in panic disorder and non-clinical panic. *Cognitive Therapy and Research, 25,* 235–246.

Robinson, B. F., Epstein, S. E., Beiser, G. D., & Braunwald, E. (1966). Control of heart rate by the autonomic nervous system. Studies in man on the interrelation between baroreceptor mechanisms and exercise. *Circulation Research, 19*(2), 400–411.

Rogeness, G. A., Cepeda, C., Macedo, C. A., Fischer, D., & Harris, W. R. (1990). Differences in heart rate and blood pressure in children with conduct disorder, major depression and separation anxiety. *Psychiatry Research, 33,* 199–206.

Rosenbaum, J. F., Biederman, J., Hirshfeld, D. R., & Bolduc, E. A. (1991). Further evidence of an association between behavioral inhibition and anxiety disorders: Results from a family study of children from a non-clinical sample. *Journal of Psychiatric Research, 25,* 49–65.

Rujescu, D., Giegling, I., Bondy, B., Gietl, A., Zill, P., & Moller, H. J. (2002). Association of anger-related traits with SNPs in the TPH gene. *Molecular Psychiatry, 7*(9), 1023–1029.

Rybakowski, F., Slopien, A., Dmitrzak-Weglarz, M., Czerski, P., Rajewski, A., & Hauser, J. (2006). The 5-HT2A-1438 A/G and 5-HTTLPR polymorphisms and personality dimensions in adolescent anorexia nervosa: Association study. *Neuropsychobiology, 53*(1), 33–39.

Sallee, F. R., Kurlan, R., Goetz, C. G., Singer, H., Scahill, L., Law, G., et al. (2000). Ziprasidone treatment of children and adolescents with Tourette's syndrome: A pilot study. *Journal of the American Academy of Child & Adolescent Psychiatry, 39,* 292–299.

Scarr, S., & Salapatek, P. (1970). Patterns of fear development during infancy. *Merrill-Palmer Quarterly, 16,* 53–90.

Schippell, P. L., Vasey, M. W., Cravens-Brown, L. M., & Bretveld, R. A. (2003). Suppressed attention to rejection, ridicule, and failure cues: A unique correlate of reactive but not proactive aggression in youth. *Journal of Clinical Child and Adolescent Psychology, 32,* 40–55.

Schmidt, N. B., Lerew, D. R., & Jackson, R. J. (1997). The role of anxiety sensitivity in the pathogenesis of panic: Prospective evaluation of spontaneous panic attacks during acute stress. *Journal of Abnormal Psychology,* 106, 355–364.

Schmidt, N. B., Storey, J., Greenberg, B. D., Santiago, H. T., Li, Q., & Murphy, D. L. (2000). Evaluating gene x psychological risk factor effects in the pathogenesis of anxiety: A new model approach. *Journal of Abnormal Psychology, 109*(2), 308–320.

Schmidt, N. B., Trakowski, J. H., & Staab, J. P. (1997). Extinction of panicogenic effects of a 35% CO2 challenge in patients with panic disorder. *Journal of Abnormal Psychology, 106,* 630–638.

Schmidt, S. M., Zoega, T., & Crowe, R. R. (1993). Excluding linkage between panic disorder and the gamma-aminobutyric acid

S___
E___
L___

beta 1 receptor locus in five Icelandic pedigrees. *Acta Psychiatrica Scandinavica, 88*(4), 225–228.

Schniering, C. A., Hudson, J. L., & Rapee, R. M. (2000). Issues in the diagnosis and assessment of anxiety disorders in children and adolescents, *Clinical Psychology Review, 20,* 453–378

Schwartz, C. E., Snidman, N., & Kagan, J. (1996). Early childhood temperament as a determinant of externalizing behavior in adolescence. *Developmental Psychopathology, 8,* 527–537.

Schwartz, C. E., Wright, C. I., Shin, L. M., Kagan, J., & Rauch, S. L. (2003). Inhibited and uninhibited infants "grown up": Adult amygdalar response to novelty. *Science, 300,* 1952–1953.

Seligman, L. D., & Ollendick, T. H. (1998). Comorbidity of anxiety and depression in children: An integrative review. *Clinical Child and Family Psychology Review, 1,* 125–144.

Shalev, A. Y., Bloch, M., Peri, T., & Bonne, O. (1998). Alprazolam reduces galvanic skin response to auditory startle in panic disorder but not in PTSD. *Biological Psychiatry, 44,* 64–68.

Silberg, J., & Bulik, C. M. (2005). Developmental association between eating disorders symptoms and symptoms of anxiety and depression in juvenile twin girls. *Journal of Child Psychology and Psychiatry, 46,* 1317–1326.

Silberg, J., Rutter, M., Neale, M., & Eaves, L. (2001). Genetic moderation of environmental risk for depression and anxiety in adolescent girls. *British Journal of Psychiatry, 179,* 116–121.

Silverman, W. K., Kurtines, W. M., Ginsburg, G. S., Weems, C. F., Lumpkin, P. W., & Carmichael, D. H. (1999). Treating anxiety disorders in children with group cognitive-behavioral therapy: A randomized clinical trial. *Journal of Consulting and Clinical Psychology, 67,* 995–1003.

Skre, I., Onstad, S., Torgersen, S., Lygren, S., & Kringlen, E. (1993). A twin study of DSM-III-R anxiety disorders. *Acta Psychiatrica Scandinavica,* 88, 85–92.

Smith, K., & Bryant, R. A. (2000). The generality of cognitive bias in acute stress disorder. *Behaviour Research and Therapy, 38*(7), 709–715.

Southam-Gerow, M. A., & Kendall, P. C. (2002). Emotion regulation and understanding: Implications for child psychopathology and therapy. *Clinical Psychology Review, 22,* 189–222.

Spence, S. H., Donovan, C., & Brechman-Toussaint, M. (1999). Social skills, social outcomes, and cognitive features of childhood social phobia. *Journal of Abnormal Psychology, 108,* 211–221.

Spence, S. H., Donovan, C., & Brechman-Toussaint, M. (2000). The treatment of childhood social phobia: The effectiveness of social skills training-based, cognitive-behavioural intervention, with and without parental involvement. *Journal of Child Psychology & Psychiatry, 41,* 713–726.

Spence, S. H., Rapee, R. M., McDonald, C., & Ingram, M. (2001). The structure of anxiety symptoms among preschoolers. *Behaviour Research and Therapy, 39,* 1293–1316.

Spielberger, C. D. (1985). *Anxiety, cognition and affect: A state-trait perspective.* Hillsdale, NJ: Lawrence Erlbaum.

Srinivasan, K., Ashok, M. V., Vaz, M., & Yeragani, V. K. (2002). Decreased chaos of heart rate time series in children of patients with panic disorder. *Depression and Anxiety, 15*(4), 159–167.

Stein, M. B., Jang, K. L., & Livesley, W. J. (1999). Heritability of anxiety sensitivity: A twin study. *American Journal of Psychiatry, 156,* 246–251.

Stein, M. B., Seedat, S., & Gelernter, J. (2006). Serotonin transporter gene promoter polymorphism predicts SSRI response in generalized social anxiety disorder. *Psychopharmacology, 187*(1), 68–72.

Stober, J. (1997). Trait anxiety and pessimistic appraisal of risk and chance. *Personality and Individual Differences, 22*(4), 465–476.

Stopa, L., & Clark, D. M. (2000). Social phobia and interpretation of social events. *Behaviour Research and Therapy, 38*(3), 273–283.

Strange, B. A., Kroes, M. C., Roiser, J. P., Tan, G. C., & Dolan, R. J. (2008). Emotion-induced retrograde amnesia is determined by a 5-HTT genetic polymorphism. *Journal of Neuroscience, 28*(28), 7036–7039.

Strauss, C. C., & Last, C. G. (1993). Social and simple phobias in children. *Journal of Anxiety Disorders,* 7, 141–152.

Strobel, A., Debener, S., Schmidt, D., Hunnerkopf, R., Lesch, K. P., & Brocke, B. (2003). Allelic variation in serotonin transporter function associated with the intensity dependence of the auditory evoked potential. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 118B*(1), 41–47.

Suetsugi, M., Mizuki, Y., Ushijima, I., Kobayashi, T., Tsuchiya, K., Aoki, T., et al. (2000). Appearance of frontal midline theta activity in patients with generalized anxiety disorder. *Neuropsychobiology, 41*(2), 108–112.

Sugiura, M., Kawashima, R., Nakagawa, M., Okada, K., Sato, T., Goto, R., et al. (2000). Correlation between human personality and neural activity in cerebral cortex. *Neuroimage, 11* (5 Pt. 1), 541–546.

Sullivan, G. M., Kent, J. M., Kleber, M., Martinez, J. M., Yeragani, V. K., & Gorman, J. M. (2004). Effects of hyperventilation on heart rate and QT variability in panic disorder pre- and post-treatment. *Psychiatry Research, 125*(1), 29–39.

Taghavi, M. R., Neshat-Doost, H. T., Moradi, A. R., Yule, W., & Dalgleish, T. (1999). Biases in visual attention in children and adolescents with clinical anxiety and mixed anxiety-depression. *Journal of Abnormal Child Psychology, 27*(3), 215–223.

Tellegen, A. (1985). Structures of mood and personality and their relevance to assessing anxiety with and emphasis on self-report. In A. H. Tuma & J. D. Maser (Eds.), *Anxiety and the anxiety disorders.* Hillsdale, NJ: Lawrence Erlbaum.

Telzer, E. H., Mogg, K., Bradley, B. P., Mai, X., Ernst, M., Pine, D. S., & Monk, C. S. (2008). Relationship between trait anxiety, prefrontal cortex, and attention bias to angry faces in children and adolescents. *Biological Psychology, 79,* 216–222.

Thapar, A., & McGuffin, P. (1995). Are anxiety symptoms in childhood heritable? *Journal of Child Psychology and Psychiatry, 36,* 439–447.

Thibodeau, R., Jorgensen, R. S., & Kim, S. (2006). Depression, anxiety, and resting frontal EEG asymmetry: A meta-analytic review. *Journal of Abnormal Psychology, 115*(4), 715–729.

Thomas, K. M., Drevets, W. C., Dahl, R. E., Ryan, N. D., Birmaher, B., Eccard, C.H., et al. (2001). Amygdala response to fearful faces in anxious and depressed children. *Archives of General Psychiatry, 58,* 1057–1063.

Ţincaş, I., Benga, O., & Fox, N. A. (2006). Temperamental predictors of anxiety disorders, *Cognition, Brain, and Behavior, 10,* 489–515.

Ţincaş, I., Dragoş, R., Ionescu, T., & Benga, O. (2007). Attentional set-shifting in preschoolers: Anxiety-related response patterns. *Cognition, Brain, and Behavior, 11,* 553–570.

Topolski, T. D., Hewitt, J. K., Eaves, L. J., Silberg, J. L., Meyer, J. M., Rutter, M., et al. (1997). Genetic and environmental influences on child reports of manifest anxiety and symptoms of separation anxiety and overanxious disorders: A community-based twin study. *Behavior Genetics, 27,* 15–28.

Toren, P., Sadeh, M., Wolmer, L., Eldar, S., Koren, S., Weizman, R., et al. (2000). Neurocognitive correlates of anxiety disorders in children: A preliminary report. *Journal of Anxiety Disorders, 14,* 239–247.

Toth, J. P., Reingold, E. M., & Jacoby, L. L. (1994). Toward a redefinition of implicit memory: Process dissociations following elaborative processing and self-generation. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 20*(2), 290–303.

Tout, K., de Haan, M., Campbell, E. K., & Gunnar, M.R. (1998). Social behavior correlates of cortisol activity in child care: Gender differences and time of day effects. *Child Development, 69,* 1247–1262.

Tracey, S. A., Chorpita, B. F., Douban, J., & Barlow, D. H. (1997). Empirical evaluation of DSM-IV generalized anxiety disorder in children and adolescents. *Journal of Clinical Child Psychology,* 26, 404–414.

Vaish, A., Grossman, T., & Woodward, A. (2008). Not all emotions are created equal: The negativity bias in social-emotional development. *Psychological Bulletin, 134,* 383–403.

Vallance, A., & Garralda, E. (2008). Anxiety disorders in children and adolescents. *Psychiatry, 7,* 325–330.

Valleni-Basile, L. A., Garrison, C. Z., Jackson, K. L., Waller, J. L., McKeown, R. E., Addy, C. L., & Cuffe, S. P. (1994). Frequency of obsessive-compulsive disorder in a community sample of young adolescents. *Journal of the American Academy of Child & Adolescent Psychiatry, 33,* 782–791.

van Leijenhorst, L., Crone, E. A., & Bunge, S. A. (2006). Neural correlates of developmental differences in risk estimation and feedback processing. *Neuropsychologia, 44*(11), 2158–2170.

Vasa, R. A., Roberson-Nay, R., Klein, R.G., Mannuzza, S., Moulton, J.L., Guardino, M., et al. (2007). Memory deficits in children with and at risk for anxiety disorders. *Depression and Anxiety, 24,* 85–94.

Vasey, M. W. (1993). Development and cognition in childhood anxiety: The example of worry. In T. H. Ollendick & R. J. Prinz (Eds.), *Advances in clinical child psychology* (Vol. 15, pp. 1–39). New York: Plenum Press.

Vasey, M. W., & Dadds, M. R. (2001). An introduction to the developmental psychopathology of anxiety. In M. W. Vasey, & M. R. Dadds (Eds.), *The developmental psychopathology of anxiety* (pp. 3–26). New York: Oxford University Press.

Vasey, M. W., Daleiden, E. L., & Williams, L. L. (1992, November). *Coping with worrisome thoughts: Strategies of anxiety-disordered and normal children.* Poster presented at the annual meeting of the Association for Advancement of Behavior Therapy, Boston.

Vasey, M. W., Daleiden, E. L., Williams, L. L., & Brown, L. M. (1995). Biased attention in childhood anxiety disorders: A preliminary study. *Journal of Abnormal Child Psychology, 23,* 267–279.

Vasey, M. W., El-Hag, N., & Daleiden, E. L. (1996). Anxiety and the processing of emotionally-threatening stimuli: Distinctive patterns of selective attention among high- and low-test-anxious children. *Child Development, 67,* 1173–1185.

Vasey, M. W., & MacLeod, C. (2001). Information processing factors in childhood anxiety: A developmental perspective. In M. W. Vasey, & M. R. Dadds (Eds.), *The developmental psychopathology of anxiety* (pp. 253–277). New York: Oxford University Press.

Visu-Petra, L., Ciairano, S., & Miclea, M. (2006). Neurocognitive correlates of child anxiety: A review of working memory research. *Cognition, Brain, and Behavior, 4,* 517–541.

Visu-Petra, L., Miclea, M., Cheie, L., & Benga, O. (2009). Processing efficiency in preschoolers' memory span: An investigation of individual differences related to age and anxiety. *Journal of Experimental Child Psychology, 101*(1), 30–48. doi:10.1016/j.jecp.2008.09.002

Visu-Petra, Ţincaş. Cheie, & Benga (in press). Anxiety and visual-spatial memory updating in young children: An investigation using emotional facial expressions. [Special issue: Emotional states, attention and working memory.] *Cognition and Emotion.*

Vrana, S. R., Roodman, A., & Beckham, J. C. (1995). Selective processing of trauma-relevant words in post-traumatic stress disorder. *Journal of Anxiety Disorders, 9,* 515–530.

Wagner, A. R., & Rescorla, R. A. (1972). Inhibition in Pavlovian conditioning: Applications of a theory. In R. A. Boakes & M. S. Halliday (Eds.), *Inhibition and learning* (pp. 301–336). New York: Academic Press.

Wang, Z. W., Crowe, R. R., & Noyes, R., Jr. (1992). Adrenergic receptor genes as candidate genes for panic disorder: A linkage study. *American Journal of Psychiatry, 149*(4), 470–474.

Watson, J. B., & Rayner, R. (1920). Conditioned emotional reactions. *Journal of Experimental Psychology, 3,* 1–14.

Watts, F. N., McKenna, F. P., Sharrock, R., & Trezise, L. (1986). Colour naming of phobia-related words. *British Journal of Psychology, 77*(Pt. 1), 97–108.

Weems, C. F., Hammond-Laurence, K., Silverman, W. K., & Ginsburg, G. S. (1998). Testing the utility of the anxiety sensitivity construct in children and adolescents referred for anxiety disorders. *Journal of Clinical Child Psychology, 27,* 69–77.

Weems, C. F., & Stickle, T. R. (2005). Anxiety disorders in childhood: Casting a nomological net. *Clinical Child and Family Psychology Review, 8*(2), 107–134.

Wells, A., & Mathews, G. (1994). *Attention and emotion: A clinical perspective.* Hillsdale, NJ: Lawrence Erlbaum.

Wendland, J. R., Moya, P. R., Kruse, M. R., Ren-Patterson, R. F., Jensen, C. L., Timpano, K. R., et al. (2008). A novel, putative gain-of-function haplotype at SLC6A4 associates with obsessive-compulsive disorder. *Human Molecular Genetics, 17*(5), 717–723.

Wiedemann, G., Pauli, P., Dengler, W., Lutzenberger, W., Birbaumer, N., & Buchkremer, G. (1999). Frontal brain asymmetry as a biological substrate of emotions in patients with panic disorders. *Archives of General Psychiatry, 56*(1), 78–84.

Wilhelm, S., McNally, R. J., Baer, L., & Florin, I. (1996). Directed forgetting in obsessive-compulsive disorder. *Behaviour Research and Therapy, 34*(8), 633–641.

AuQ5

S___
E___
L___

Williams, J. M., Mathews, A., & MacLeod, C. (1996). The emotional Stroop task and psychopathology. *Psychological Bulletin, 120*(1), 3–24.

Williams, J. M., Watts, F. N., MacLeod, C., & Mathews, A. (1988). *Cognitive psychology and emotional disorders.* Chichester, UK: Wiley.

Wilson, E. J., & MacLeod, C. (2003). Contrasting two accounts of anxiety-linked attentional bias: Selective attention to varying levels of stimulus threat intensity. *Journal of Abnormal Psychology, 112*(2), 212–218.

Wilson, E. J., MacLeod, C., Mathews, A., & Rutherford, E. M. (2006). The causal role of interpretive bias in anxiety reactivity. *Journal of Abnormal Psychology, 115*(1), 103–111.

World Health Organization. (1992). *The ICD-10 classification of mental and behavioral disorders.* Geneva: Author.

Wray, N. R., James, M. R., Dumenil, T., Handoko, H. Y., Lind, P. A., Montgomery, G. W., et al. (2008). Association study of candidate variants of COMT with neuroticism, anxiety and depression. *American Journal of Medical Genetics Part B*: *Neuropsychiatric Genetics*

Yamasue, H., Abe, O., Suga, M., Yamada, H., Inoue, H., Tochigi, M., et al. (2008). Gender-common and -specific neuroanatomical basis of human anxiety-related personality traits. *Cerebral Cortex, 18*(1), 46–52.

Yeragani, V. K., Pohl, R., Balon, R., Ramesh, C., Glitz, D., Jung, I., et al. (1991). Heart rate variability in patients with major depression. *Psychiatry Research, 37*(1), 35–46.

Yeragani, V. K., Pohl, R., Srinivasan, K., Balon, R., Ramesh, C., & Berchou, R. (1995). Effects of isoproterenol infusions on heart rate variability in patients with panic disorder. *Psychiatry Research, 56*(3), 289–293.

Young, S. E., Smolen, A., Stallings, M. C., Corley, R. P., & Hewitt, J. K. (2003). Sibling-based association analyses of the serotonin transporter polymorphism and internalizing behavior problems in children. *Journal of Child Psychology and Psychiatry, 44*, 1–7.

Zetzsche, T., Preuss, U. W., Bondy, B., Frodl, T., Zill, P., Schmitt, G., et al. (2008). 5-HT1A receptor gene C-1019 G polymorphism and amygdala volume in borderline personality disorder. *Genes, Brain and Behavior, 7*(3), 306–313.

Zoellner, L. A., Foa, E. B., Brigidi, B. D., & Przeworski, A. (2000). Are trauma victims susceptible to "false memories"? *Journal of Abnormal Psychology, 109*(3), 517–524.