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The Origins of Neuroticism

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Abstract
In this article, we provide a fresh perspective on the developmental origins of *neuroticism*—a dimension of temperament marked by elevated stress reactivity resulting in the frequent experience of negative emotions. This negative affectivity is accompanied by a pervasive perception that the world is a dangerous and threatening place, along with beliefs about one's inability to manage or cope with challenging events. Historically, neuroticism has been viewed as a stable, genetically based trait. However, recent understanding of ongoing gene–environment interactions that occur throughout the life span suggests there may be a more complex and dynamic etiology. Thus, the purpose of this article is to offer a theory for understanding the development of neuroticism that integrates genetic, neurobiological, and environmental contributions to this trait. Given the strong correlation between neuroticism and the development of negative health outcomes—most notably, the full range of anxiety and mood disorders—an enhanced understanding of how neuroticism originates has implications for the treatment and prevention of a broad range of pathologies and, perhaps, even for the prevention of neuroticism itself.

Keywords
neuroticism, temperament

Understanding and describing *temperament*—an individual's emotional nature—has long been of interest dating back as far as 450 BCE when Greek physicians described four "humors" (blood, black bile, yellow bile, and phlegm) that were thought to contribute to an individual's characteristic emotional style (e.g., a melancholic or gloomy temperament resulting from high levels of black bile; Digman, 1994). Modern conceptualizations also emphasize that emotions are at the core of understanding one's temperament (Clark & Watson, 2008). The neurotic temperament, which incorporates the tendency to react negatively in response to various sources of stress, has been a particular focus of attention. The negative emotions usually considered integral to this trait include anxiety, fear, irritability, anger, and sadness. In addition to exaggerated negative emotionality, neurotic temperament (or neuroticism) is also characterized by the pervasive perception that the world is a dangerous and threatening place, along with beliefs about one's inability to manage or cope with challenging events (Barlow, 2002; Barlow, Sauer-Zavala, Carl, Bullis, & Ellard, 2014; Clark & Watson, 2008; Eysenck, 1947; Goldberg, 1993). Thus, we define *neuroticism* as the tendency to experience frequent, intense negative emotions associated with a sense of uncontrollability (the perception of inadequate coping) in response to stress. This definition of neuroticism does not include processes such as worry, rumination, or emotional avoidance, though these processes likely follow from high levels of neuroticism and maintain it (see Barlow et al., 2014).

Given the public health implications of high levels of neuroticism observed in the population (for a review, see Lahey, 2009), it is not surprising that this trait has been the focus of intensive theorizing and research. For example, neuroticism is strongly associated with and predicts a variety of mental disorders, including comorbidity (Clark, Watson, & Mineka, 1994; Khan, Jacobson, Gardner, Prescott, & Kendler, 2005; Krueger & Markon, 2006; Sher & Trull, 1994; Weinstock & Whisman, 2006), and these relationships remain significant in longitudinal studies in which concurrent depressive states are controlled for (Spijker, de Graaf, Oldehinkel, Nolen, & Ormel, 2007).

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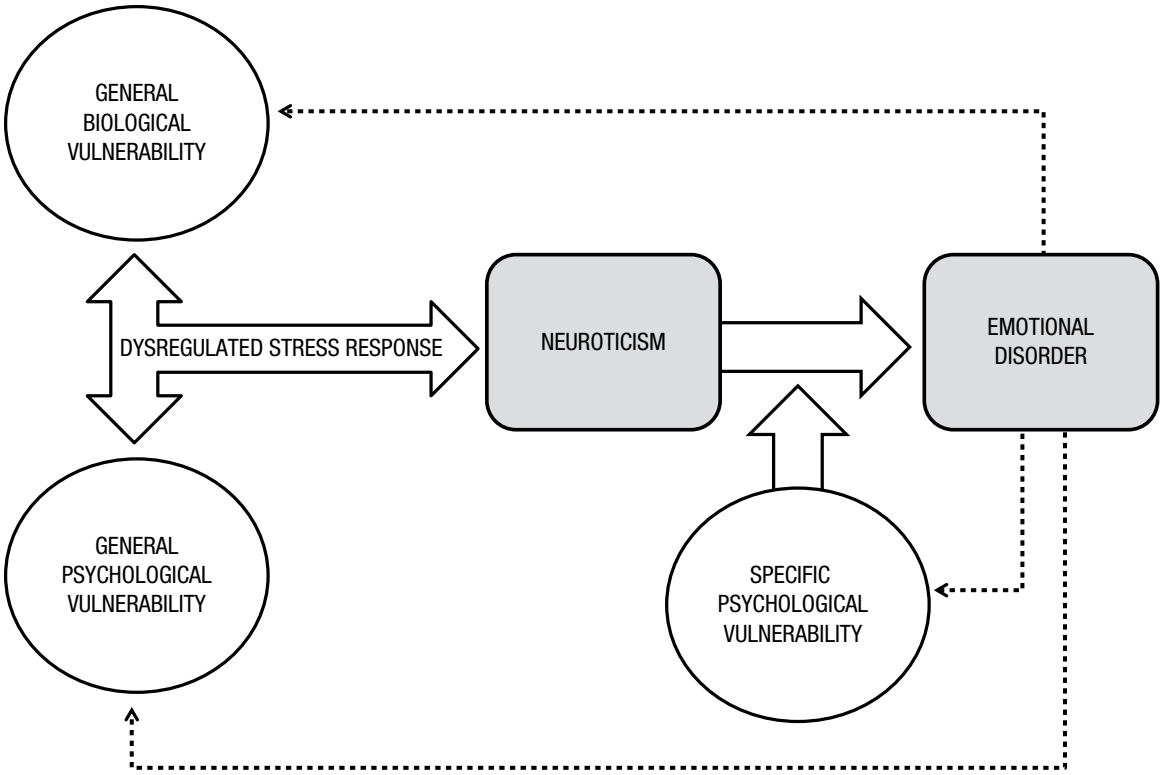

Fig. 1. The revised triple vulnerability theory in the development of neuroticism and emotional disorders specifying synergistic biological and psychological vulnerabilities. The figure represents the primary developmental pathway for neuroticism and emotional disorders through the bidirectional interaction between the two general vulnerabilities and the moderation effect of the specific psychological vulnerability on the expression of neuroticism. The secondary influence of emotional disorders on the general vulnerabilities via a negative feedback cycle is also represented.

Perhaps less obvious is the link between neuroticism and physical health; indeed, this trait has been associated with a range of physical problems, including cardiovascular disease, eczema, asthma, and irritable bowel syndrome (Brickman, Yount, Blaney, Rothberg, & De-Nour, 1996; Smith & MacKenzie, 2006; Suls & Bunde, 2005). Neuroticism also predicts treatment seeking and response to treatment for both mental disorders and general health concerns (Shipley, Weiss, Der, Taylor, & Deary, 2007). Considering these public health consequences, Cuijpers et al. (2010) estimated that the economic cost of neuroticism in a large representative sample of the Dutch population exceeded the cost of common mental disorders.

The purpose of the present article is to articulate a theory for understanding the development of neuroticism that integrates genetic, neurobiological, and environmental contributions to this trait. Given the relationship between neuroticism and psychopathology (described earlier), we believe that cultivating a better understanding of how neuroticism develops has implications for the treatment and, more basically, the prevention of emotional disorders, such as anxiety and mood disorders (Barlow et al., 2014). This approach is consistent with the National Institute of Mental Health's Research Domain Criteria initiative that challenges researchers to look beyond diagnoses to identify core processes implicated in the development and maintenance of symptoms across a range of disorders (Insel et al., 2010). Thus, neuroticism itself becomes a valid target for treatment, and understanding its origins provides a framework for how this might happen.

Triple Vulnerability Theory

It is our evolving view that *triple vulnerability theory* (Barlow, 1991, 2002), originally proposed to describe the emergence of anxiety and mood disorders, actually better depicts the development of neuroticism itself. A visual depiction of how our revised conception of the triple vulnerabilities accounts for this development is presented in Figure 1. Specifically, triple vulnerability theory describes three separate but interacting *diatheses* or vulnerabilities (Barlow, 1988, 2000). These include a general biological (heritable) vulnerability, a general psychological vulnerability consisting of a heightened sense of unpredictability and uncontrollability and associated

changes in brain function resulting from early adverse experience, as well as a more specific psychological vulnerability—also largely learned—accounting for why one particular emotional disorder (e.g., panic disorder) may emerge instead of another (e.g., obsessive-compulsive disorder). In our conceptions, the two general vulnerabilities identified in the triple vulnerability theory dynamically contribute to the development and expression of neuroticism itself (Brown & Barlow, 2009; Suárez, Bennett, Goldstein, & Barlow, 2009), which, in turn, mediates risk for the development of anxiety, mood, and related emotional disorders, as described later.

General biological vulnerability

The general biological risk factor is defined largely by genetic and neurobiological contributions to personality traits or temperament styles (Barlow, 2000).[1] As noted earlier, triple vulnerability theory originated in the context of the development of trait anxiety and emotional disorders; furthermore, a genetic link to emotional disorders has been well established in both family and twin studies (e.g., Hettema, Neale, & Kendler, 2001; Skre, Onstad, Torgersen, Lygren, & Kringlen, 1993). Neuroticism is also heritable, with genetic contributions estimated as composing between 40% and 60% of the variance in the expression of this trait (e.g., Bouchard & Loehlin, 2001; Clark et al., 1994; Kendler, Prescott, Myers, & Neale, 2003). Much of this work has been done by examining self-report personality measures in twins, with results consistently showing that genetics account for nearly half of the variance in predicting personality, that shared environmental effects (such as parental socioeconomic status and religious traditions) predict almost nothing, and that nonshared environmental effects (different teachers, leisure activities, life events) account for the remaining variance (Turkheimer, 2000). In recent work, researchers have demonstrated that the influence of genetic contributions to neuroticism is stronger for younger individuals, whereas the environment appears to exert more influence in older adults (Laceulle, Ormel, Aggen, Neale, & Kendler, 2013). That is, after emerging in childhood, neuroticism remains relatively stable before showing gradual age-related decreases that continue into old age (Eaton, Krueger, & Oltmanns, 2011; Roberts & Mroczeck, 2008; Roberts, Walton, & Viechtbauer, 2006), with great variability across individuals in terms of the magnitude of this change (Helson, Jones, & Kwan, 2002; Mroczek & Spiro, 2003; Small, Hertzog, Hultsch, & Dixon, 2003). Indeed, as people age, any continuity in the expression of neuroticism appears to result from cumulative environmental effects, underscoring the importance of interactions between genetically mediated physiology and the environment (described in detail in the paragraphs that follow; Kandler et al., 2010).

The genetic components of neuroticism are linked to the neurobiological tendency for heighted reactivity in emotion generating structures, most notably amygdala hyperexcitability, and reduced or inefficient inhibitory control by prefrontal structures (Keightley et al., 2003; Stein, Simmons, Feinstein, & Paulus, 2007; Westlye, Bjornebekk, Grydeland, Fjell, & Walhovd, 2011). Exaggerated amygdala responses are linked to a functional polymorphism in the promoter region of the serotonin transporter gene (5HTTPR), with people who are homozygous for the low-expressing genotype (having two short alleles) showing greater magnitude of amygdala responses to emotional stimuli (Drabant et al., 2012; Lonsdorf et al., 2011; Munafo, Brown, & Hariri, 2008) as well as reductions in functional connectivity between emotion-generating regions (e.g., amygdala) and structures implicated in their inhibitory control (e.g., ventromedial prefrontal cortex; Pezawas et al., 2005). The presence of this s/s allele functional polymorphism is independently associated with neuroticism (Lesch et al., 1996; Montag, Basten, Stelzel, Fiebach, & Reuter, 2010; Stein, Campbell-Sills, & Gelernter, 2009) and also with the development of psychopathology following life stressors (Caspi et al., 2003; Owens et al., 2012). These results should be interpreted with caution, however, as researchers of large-scale studies examining the effects of this functional polymorphism have yielded mixed results or have failed to replicate these findings (Terracciano et al., 2009). Nevertheless, one pathway to the development of neuroticism may be a genetically mediated hyperexcitability to aversive or potentially threatening stimuli and a reduced ability to normalize activation once the threat diminishes or threat-related contingencies change.

It is important to note that this hyperexcitability of neural circuits in response to stress and fear results not only from genetic factors or biological predispositions but also from stressful or traumatic experiences during critical stages of development (Gunnar & Quevedo, 2007; Lanius, Frewen, Vermetten, & Yehuda, 2010; Rosen & Schulkin, 1998); that is, early adversity sculpts the stress response that seems to underpin the neurotic phenotype (Francis, Champagne, Liu, & Meaney, 1999; Liu et al., 1997). Additionally, physiological reactivity to stressors (e.g., heightened arousal) is not in-and-of-itself a marker of neuroticism; in fact, arousal responses essentially represent an adaptive capability that enables individuals to mount the necessary and context appropriate behavioral responses to a stressor. It is when the arousal response system misfires—either in the wrong context or at a very exaggerated level—that pathology emerges. Thus, biology alone does not lead to maladaptive endpoints; rather,

it is the combination of heightened physiological reactivity with a psychological perception of the unpredictability or uncontrollability of the stressor that leads to the development of neuroticism (e.g., Koolhaas et al., 2011), a point to which we now turn.

General psychological vulnerability

The general psychological vulnerability, again originally conceptualized as important for the development of emotional disorders, can be characterized as a pervasive sense of unpredictability and uncontrollability in relation to life events and a perceived inability to cope with negative outcomes from such life events (Barlow, 2000, 2002). Although much of this research has focused on examining relationships between these constructs and specific anxiety or depressive disorders, recent work highlighting the role of neuroticism as a latent factor underlying these disorders leads us to now hypothesize that experiences with unpredictability and uncontrollability may be important factors in the development of neuroticism itself. In this subsection, we review evidence related to the role of perceptions of controllability and predictability in the development and expression of neuroticism.

Basic animal research. Laboratory research in which anxious apprehension is provoked in animals suggests how environmental factors that produce a sense of uncontrollability over stressful events can influence the development of neuroticism. An extensive body of research dating back to Pavlov (1927) has shown that conditions such as excessive punishment of appetitive responses, deprivation, and presentation of insoluble tasks accompanied by punishment of mistakes can produce signs of extreme anxiety, including increased autonomic arousal, excessive motor activity, and attentional and performance impairments (Liddell, 1949; Masserman, 1943). Such experimentally induced anxiety in animals was termed *experimental neurosis*. In reviewing the experimental neurosis literature, Mineka and Kihlstrom (1978) made the important observation that across studies with different methodologies, the conditions that induced (chronically) anxious behavior in animals were those that produced a sense of unpredictability and uncontrollability. On the basis of this finding, the authors hypothesized that such a sense of unpredictability and uncontrollability over important life activities may be the common factor in promoting the development of experimental neurosis.

Mineka and others also conducted studies designed to explore more specifically the relationship among predictability, controllability, and neuroticism. In line with expectations, researchers found that higher versus lower predictability and controllability of stressful events mitigated or exacerbated, respectively, subsequent levels of negative emotions (Mineka, Cook, & Miller, 1984; Seligman, 1975). The effects of a sense of control on behavioral and physiological outcomes have also been examined in relation to appetitive-oriented situations within samples of rhesus monkeys; results indicated that monkeys raised with greater control over appetitive goals (i.e., food acquisition) responded more actively and with decreased cortisol reactivity when presented with novel situations compared with monkeys that were allowed less control over food access (Roma, Champoux, & Suomi, 2006). Relatedly, infant monkeys who were raised by mothers experiencing unpredictable foraging conditions exhibited greater levels of corticotropin-releasing hormone (CRH) than infant monkeys raised by mothers experiencing either a consistent overabundance or a consistent scarcity of food (Coplan et al., 1996). This finding suggests that the elevated levels of stress hormones were not the result of a lack of food in and of itself but rather the unpredictable nature of the food supply. Similarly, researchers conducting seminal studies of baboons in the wild found that those baboons whose ranking within the social hierarchy was either uncertain or under challenge by other baboons exhibited the highest levels of cortisol output (Sapolsky, 1990; Sapolsky, Romero, & Munck, 2000). High cortisol concentrations were not associated with instability of interactions with the population as a whole but rather were associated with the degree of instability of interactions among male baboons close in rank, because the outcome of these challenges were relatively unpredictable and uncontrollable, but the potential consequences for social status were high (Gesquire et al., 2011; Sapolsky, 1992). These findings suggest that an elevated sense of controllability is not only important for developing healthy response tendencies in relation to inevitable aversive events in life but also for cues related to positive goals.

Basic human research. In studies with humans, individual differences in perception of control have been shown to affect mental health outcomes (Barlow, 2002; Chorpita & Barlow, 1998). An extensive body of research regarding the construct *locus of control* (Rotter, 1966) has indicated that individuals who report a more external versus internal locus of control are more likely to score more highly on neuroticism scales (McCauley, Mitchell, Burke, & Moss, 1988; Nunn, 1988; Siegel & Griffin, 1984; Skinner, Chapman, & Baltes, 1988; Weisz & Stipek, 1982; White, Brown, Somers, & Barlow, 2006; Wiersma et al., 2011). Additionally, in a meta-analysis of more than 100 independent studies comprising 8,251 individuals, Miller, Chen, and Zhou (2007) found that uncontrollable, unpredictable stressors led to both higher and less variable levels of daily cortisol output relative to stressors that were more controllable or predictable.

The study of cognitive styles also provides some additional evidence in support of the importance of a sense of control in the experience of negative emotions. Again, findings indicate that a negative attributional style in which one tends to attribute negative events to global, stable, and internal reasons is associated with anxiety (Chorpita, Brown, & Barlow, 1998; Cole, Peeke, Martin, Truglio, & Seroczynski, 1998) and depression (Nolen-Hoeksema, Girgus, & Seligman, 1992) in older children and adults. However, other research indicates that negative cognitive styles may be more closely related to neuroticism than to the development of specific diagnoses of depression or specific anxiety disorders (Alloy et al., 2012; Luten, Ralph, & Mineka, 1997). This finding lends some support to the notion that a sense of controllability functions more as a general psychological vulnerability for the development of neuroticism than as a specific risk factor for certain emotional disorders.

Parenting styles and perceptions of control. Parenting styles also appear to be closely implicated in the development of perceptions of control (Chorpita & Barlow, 1998; McLeod, Wood, & Weisz, 2007; van der Bruggen, Stams, & Bögels, 2008). In the attachment literature, researchers identify key parenting behaviors that have the potential to increase or decrease a child's sense of his/her own degree of control over life events. These include behaviors such as warmth and consistency, which foster a sense of security and predictability in the world (Bowlby, 1980). In a recent longitudinal study, results revealed that low maternal responsiveness during infancy was associated with children reporting a less well-developed perceived sense of control over their environment at 11 years of age (Dan, Sagi-Schwartz, Bar-Haim, & Eshel, 2011). Promotion of independence in the context of positive attachment also enhances the child's sense of self-efficacy and ability to cope with life events (Barlow, 2002; Bowlby, 1980; Chorpita, 2001; Thompson, 1998). In contrast, intrusive and controlling parenting behaviors (so called "snowplow" or "helicopter" parenting) tend to decrease a child's perception of control (Chorpita & Barlow, 1998).

Although the majority of research in this area has focused on the relationships between parenting styles and the development of anxiety (Hudson & Rapee, 2002; Rubin, Coplan, & Bowker, 2009; van der Bruggen et al., 2008) and depression (Ingram & Ritter, 2000; Reiss et al., 1995), there is evidence that parenting styles moderate the effects of early vulnerabilities on stress reactivity and emotionality more generally (Chorpita & Barlow, 1998). That is, in monkeys and in humans, positive parenting behaviors, as described earlier, can buffer against the development of neuroticism. In rhesus monkeys, babies with high stress reactivity, believed to reflect a general biologic vulnerability, have been found to become substantially less reactive when raised by mothers with low stress reactivity in cross-rearing paradigms (Suomi, 1999, 2000). In contrast, when reared by mothers with high stress reactive, such babies remain highly reactive. In 9-month-old human babies, increased cortisol levels in response to separation from mothers diminish when babies are returned to responsive caregivers, but they remain elevated when returned to nonresponsive caregivers (Gunnar, Larson, Hertsgaard, Harris, & Brodersen, 1992). More broadly, harsh or intrusive and overcontrolling parenting styles (snowplow or helicopter parenting) may produce lasting disruptions in children's hypothalamic-pituitary-adrenal (HPA) axis functioning (Gunnar & Donzella, 2002; Murray, Halligan, Goodyer, & Herbert, 2010; Shea, Walsh, MacMillan, & Steiner, 2005), including higher resting cortisol (Taylor et al., 2012). In addition to negative parenting behaviors, varieties of early adverse experiences—including child physical or sexual abuse, child family dysfunction, and physical or emotional neglect—have been directly associated with higher levels of neuroticism in adult offspring (Kendler & Gardner, 2011; Roy, 2002). Although more research is needed to understand the mechanisms through which such experiences contribute to neuroticism, we suggest that inadequate development of perceptions of control is strongly implicated.

Summary. In summary, findings from a number of areas of research, including both animal and human studies, support the key role of a sense of unpredictability and uncontrollability in the development of trait anxiety or neuroticism. A diminished sense of predictability and controllability appears to adversely affect stress hormone functioning in children, which, in turn, is associated with persistent state of negative emotionality. Early adversity and parenting behaviors have been shown to influence children's perceptions of control—and associated cognitive styles—therefore increasing their risk or resilience to stress. Rather than conferring direct risk for the development of specific anxiety or depressive disorders, these environmental variables may moderate risk for a persistent state of negative emotionality or neuroticism, which, in turn, increase the probability of developing anxiety and mood disorders.

Interactions between general biological and psychological vulnerabilities

In discussing general biological and psychological vulnerabilities, it is important to note that we cannot conclusively make a determination of the cause-and-effect relationship between these vulnerabilities and neuroticism. Rather than a static, one-directional relationship, it

is more accurate to conceptualize a dynamic, interacting relationship among these constructs. Environmental stressors interact with biological vulnerabilities described earlier in a bidirectional manner to influence dispositional levels of neuroticism, such that an individual with a genetic predisposition toward greater reactivity to stress may be more susceptible to the detrimental impact of stress and trauma, exhibiting a decreased capacity to cope and greater negative impact as a result of such stressors. Further, whereas genetic factors may predispose a lowered threshold for reactivity at the neural level (e.g., greater limbic reactivity), repeated exposure to stressful environmental contexts may potentiate these responses through a process of "sensitization" (Charney, Deutch, Krystal, Southwick, & Davis, 1993; Figueiredo, Bodie, Tauchi, Dolgas, & Herman, 2003; Rosen & Schulkin, 1998). Long-term potentiation of fear circuitry through repeated activation sensitizes this system, leading to hypervigilance and greater reactivity to threat (Lanius et al., 2010). Repeated or prolonged exposure to stressors produces a "kindling" effect, whereby neural reactivity to stress-related stimuli becomes more diffuse and widespread (Gelowitz & Kokkinidis, 1999). This kindling effect sets in motion a series of effects—including the expression of *immediate early genes* (IEGs)[2] in limbic structures (Campeau et al., 1997; Shin, McNamara, Morgan, Curran, & Cohen, 1990)—and plays a crucial role in brain development across the life span. However, how do psychological and environmental factors play a role in these processes?

HPA axis as a model of biological/psychological/environmental interactions. Repeated exposure to stress, particularly during early experience, has been linked to molecular and morphological changes in brain circuits mediating stress responses, and it is associated with exaggerated responses to subsequent threatening or fearful stimuli (Cowen, 2010; Rosen & Schulkin, 1998; Tafet & Bernardini, 2003). In particular, associations between chronic stress and aberrant functioning of the HPA axis modulating stress responses have been well established (Essex et al., 2011; Gillespie, Phifer, Bradley, & Ressler, 2009; Gunnar & Quevedo, 2007; Heim & Nemeroff, 1999; Miller et al., 2007; Sapolsky et al., 2000) and represent a cogent model to illustrate the interactions among environmental, psychological, and biological factors in the development of neuroticism.

The HPA axis serves to regulate the body's reaction to stress in the service of mounting an appropriate behavioral response through the secretion of stress hormones (glucocorticoids). One of the most studied of these stress hormones is cortisol, which functions to modulate the body's response to threat through its influence on widespread bodily systems—including cardiovascular, digestive, and immunological systems—as well as key neural systems influencing learning, memory, emotion, and attentional control (Radley, 2012; Sapolsky et al., 2000). Under normal adaptive conditions, the output of cortisol is regulated through a negative feedback loop to the hippocampus, which suppresses the production of cortisol once excess levels are detected, thereby maintaining adaptive allostasis. However, excessive hypersecretion of cortisol and other stress hormones under conditions of chronic stress serves to overwhelm this system, pushing the organism toward an allostatic load wherein the stress responses are activated without sufficient recovery (Gunnar & Quevedo, 2007). The inability to inhibit the production of these hormones may be due to the fact that, at high levels resulting from chronic stress, they become neurotoxins that destroy the very brain structures (e.g., hippocampus) required to suppress them while preventing adequate neurogenesis in the hippocampus (Conrad, 2008; Magarinos & McEwen, 1995).

Effects of stress-related changes in neural function. Stress-related alterations in neural network structure and function may underlie much of the vulnerability for pathology seen across emotional disorders. As mentioned earlier, neuroticism has been linked to the neurobiological tendency toward heightened limbic reactivity and deficient cortical regulation of limbic activation, representing the neurobiological correlate of emotion dysregulation (Keightley et al., 2003; Stein et al., 2007; Westlye et al., 2011). To take one example, stress-related reductions in hippocampal neurogenesis have recently been linked to the overgeneralization of fear in emotional disorders. Deficient neurogenesis is associated with impairments in the ability of hippocampal structures to encode distinct memory traces, a process referred to as *pattern separation* (Deng, Almone, & Gage, 2010; Tronel et al., 2012). Pattern separation during memory encoding is crucial to the ability to distinguish between similar sensory inputs and contexts, such that information specific to a stimulus or context can be retrieved. Thus, impairments in pattern separation during memory encoding can lead to information about two distinct yet similar stimuli being encoded and retrieved as indistinguishable from one another. Impaired pattern separation thus may underlie the tendency toward overgeneralization of fear across multiple contexts (e.g., fear triggered by the sound of a helicopter both on and off the battlefield; Kheirbek, Klemenhagan, Sahay, & Hen, 2012; Sahay et al., 2011).

Effects of chronic stress and HPA axis dysfunction across the life span. The long-term effects of chronic stress and HPA axis dysfunction on patterns of neural organization and function are only beginning to be

clarified. For example, Burghy et al. (2012) found that exposure to early life stress was significantly associated with higher cortisol levels during the school-age years and predicted lower resting state functional connectivity between the amygdala and ventromedial prefrontal cortex at 18 years of age. As noted earlier, the amygdala–ventromedial prefrontal cortex pathway is a critical cortico-limbic pathway for the regulation of fear and anxiety (Delgado et al., 2008; Milad et al., 2007; Ochsner et al., 2002, 2004; Phelps et al., 2004). Thus, this study provides preliminary empirical evidence for a developmental sequence wherein early exposure to chronic stress and associated HPA axis functioning affects later brain development and organization in neural regions key to the adaptive regulation of negative emotions.

Evidence suggests that the impact of chronic stress and trauma on HPA axis functioning is far reaching across the life span. Early disruptions in parent–child relationships described earlier (one early source of a sense of uncontrollability) result in higher cortisol levels by preschool age, and these higher levels in turn predict increased behavioral and emotional problems by school age (Essex, Klein, Cho, & Kalin, 2002). Relative to securely attached infants, infants with a disorganized attachment status show elevated cortisol levels during separation from their primary caregiver as well as slow return to baseline cortisol levels after being reunited (Hertsgaard, Gunnar, Erickson, & Nachmias, 1995). In multiple investigations, researchers have linked early life stress, childhood maltreatment, or childhood physical or sexual trauma to elevated cerebrospinal fluid concentrations of CRH (Cicchetti & Rogosch, 2001; Gunnar & Quevedo, 2007; Heim & Nemeroff, 1999; Rogosch, Dackis, & Cicchetti, 2011).

Heim and Nemeroff (1999) have suggested that early traumatic experiences may lead to an initial sensitization of the stress hormone system leading to increased CRH secretion, followed by eventual blunted adrenocorticotropic hormone secretion in an attempt to downregulate excessive CRH, and that this aberrant function of the HPA axis represents a vulnerability to experience frequent, strong negative emotions.

Hyper- versus hypocortisolism and neuroticism. Although traditional models have supposed an association among chronic stress, neuroticism, and elevated levels of circulating cortisol, contradictory evidence exists, finding both hypercortisolemia and hypocortisolemia associated with neuroticism and depression. This evidence has led to some confusion in the literature regarding the role of HPA dysfunction in neuroticism. For example, in one study, higher scores on the personality dimension of neuroticism were associated with blunted cortisol responses to stress in women (Oswold et al., 2006), and in a second study, findings revealed lower adrenocorticotropic hormone and cortisol output in individuals with high negative emotionality relative to individuals with low negative emotionality (Jezova, Makatsori, Duncko, Moncek, & Jakubek, 2004). However, Duncko, Makatsori, Fickova, Selko, and Jezova (2006) found evidence to suggest neuroticism is not associated with global hyper- or hyporesponsiveness along the HPA axis per se, but rather individuals high in neuroticism evidence alterations in the coordination of neuroendocrine responses to stress and may exhibit more rigid, inflexible diurnal rhythms (Doane et al., 2013). These findings are consistent with recent conceptualizations of stress reactivity, which suggest that it is not the overall magnitude of the response to stimuli that constitutes a stress response but rather the ability to recover to baseline following exposure to stress (Koolhaas et al., 2011).

A meta-analysis of more than 100 studies by Miller et al. (2007) sheds further light on the apparent inconsistencies in the literature with regards to hyper- versus hypocortisolemia in neuroticism. They found evidence to support the co-occurrence of both hyper- and hypocortisolemia related to chronic stress, trauma, anxiety and depression, identifying several factors that mediated cortisol output, including time since the onset of the chronic stressor, the specific type of chronic stressor, and the controllability of the stressor. First, time since the onset of the stressor was negatively correlated with HPA axis reactivity, such that immediately present stressors elicited significantly higher daily cortisol output, whereas more distant trauma elicited significantly lower morning cortisol output. These findings are consistent with hypotheses suggesting initial sensitization of stress responses followed by eventual blunting of responses when the individual reaches allostatic load. Second, stressors that involve threats to physical integrity or stressors that are perceived as uncontrollable elicit a high and flat diurnal pattern of cortisol output, characterized by lower than normal morning output, higher than normal afternoon and evening output, and greater overall daily output volume. This finding suggests that measures of cortisol output depend on (a) the proximity of the stressor, (b) the type of stressor, and (c) the time of day in which measurements of cortisol output are taken. Blunted or hyporeactive responses of stress hormones may also represent avoidant processing of stress-related cues (Duncko et al., 2006). In a recent confirmatory factor analysis of cortisol output in posttraumatic stress disorder, Horn, Pietrzak, Corsi-Travali, and Neumeister (2014) found blunted cortisol levels to be independently related to severity of trauma-related numbing symptoms, suggestive of avoidant processing. Future research is needed to clarify this relationship.

Summary. Taken together, the origins of neuroticism may arise out of a combination of genetic factors, which predispose the individual to greater reactivity to threat or stress, coupled with early environmental experiences of chronic stress or trauma or parenting styles that increase a sense of control and blunt the development of resilience. These factors are consistent with the triple vulnerability theory's general biological and psychological risk factors. The combination of genetic factors and early adverse experiences emanating from a number of sources sensitizes key circuits within the brain in response to acute stress, leading to altered stress reactivity. This process in turn affects neural development and organization with long-term effects on the way an individual processes and responds to threat-related information, both of which are defining characteristics of neuroticism.

Specific psychological vulnerability: The development of emotional disorders

The third component of the triple vulnerability theory refers to specific psychological factors that explain why a particular emotional disorder may emerge from a high level of neuroticism conferred through the general biological and psychological vulnerabilities described earlier (see Figure 1). That is why some people high in neuroticism may develop one disorder, such as panic disorder, whereas others—similarly high in neuroticism—develop another disorder, such as obsessive-compulsive disorder.

In our view, the co-occurrence of general biological and psychological vulnerabilities may be sufficient to result in the development of generalized anxiety disorder, thought to be the phenotypic expression of high levels of neuroticism (Brown, Barlow, & Liebowitz, 1994). Additionally, depression represents the expression of high levels of neuroticism coupled with a low degree of positive affect associated, perhaps, with particularly low resilience (Abramson, Metalsky, & Alloy, 1989; Alloy et al., 2012). The pathway to other emotional disorders as currently conceptualized in the *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.; American Psychiatric Association, 2013) classification system, however, may depend on the development of specific foci for anxiety or distress. In other words, the pathway from neuroticism to disorders other than generalized anxiety disorder and depressive disorders may depend on learning experiences that create conditions for a specific focus of anxious or fearful reactions. Several types of learning experiences may come into play. For example, direct aversive experiences with an object, situation, or context can result in classical conditioned fear and anxiety responses. Also, there is evidence to suggest that observational learning and behavioral modeling by primary caregivers or other close associates may be contributory. In an early large study in which pathways to fear acquisition in American and Australian children and adolescents were investigated, the majority of respondents attributed the onset of their fear to vicarious and instructional factors, although those who endorsed a high level of fear also endorsed direct conditioning experience in combination with these sources (Ollendick & King, 1991).

Evidence for the observational learning of fear comes from both animal models and human studies. For example, early studies showed that laboratory-reared rhesus monkeys who were not initially afraid of snakes acquired intense fear responses after spending several sessions observing wild-reared monkeys exhibit fear in the presence of snakes (Cook, Mineka, Wolkenstein, & Laitsch, 1985; Mineka, Davidson, Cook, & Keir, 1984). Similar effects have been observed in humans (Gerull & Rapee, 2002). In this study, toddlers observed their mother's reaction to a toy snake or toy spider. The mothers displayed negative reactions to one toy and displayed neutral reactions to the other. Toddlers displayed significantly greater avoidance behavior in the presence of objects to which their mothers displayed fear or disgust expressions than to neutral-reaction objects, suggesting the toddlers acquired a conditioned association through observing their mother's reactions.

Because of the ethical concerns surrounding laboratory studies of acquired fear in children, few laboratory studies of the transmission of anxiety or fear directly related to psychological disorders through observational learning have been conducted. However, researchers using retrospective report in their studies lend support to the idea that the development of pathological fear and anxiety may be the result of observational learning experiences. This type of evidence is strongest for panic disorder. For example, patients with panic disorder recalled more parental encouragement of sick-role behavior in response to panic-related symptoms (e.g., racing heart, dizziness, shortness of breath, or strong nausea) during childhood relative to control participants, whereas no differences between groups were found in parental encouragement of sick-role behavior in response to cold symptoms (Ehlers, 1993). In another study, Watt, Stewart, and Cox (1998) also found that anxiety sensitivity that reflected anxiety associated with somatic symptoms was positively related to parental encouragement of sick-role behavior in response to somatic symptoms. Relatedly, individuals whose relatives had chronic obstructive pulmonary disease while growing up were more likely than those who did not to have a specific sensitivity to interpreting their own respiratory symptoms as potentially hazardous (Craske, Poulton, Tsao, & Plotkin, 2001). These results are consistent with the findings that a history of physical diseases differentiated women diagnosed with

panic disorder from women with social anxiety disorder; patients with panic disorder may have learned in childhood that unexpected bodily sensations are dangerous—a specific vulnerability for panic disorder (Rudaz, Craske, Becker, Lederman, & Margraf, 2010).

The interaction of early specific learning experiences and neuroticism is only beginning to be understood. In one compelling study, participants learned object–emotion associations by observing specific facial expressions (portraying fear, happiness, or a neutral expression) paired with specific objects. Fear association learning relative to neutral or reward association learning resulted in greater amygdala–hippocampus activation, and this effect was modulated by temperament. Specifically, neuroticism was positively related to the degree of amygdala and hippocampus activation during fear learning, and, in turn, greater amygdala–hippocampus activation during fear learning was associated with better long-term memory of learned associations. Greater neuroticism also predicted faster behavioral response times in participants when both predicting and recognizing fear expressions (Hooker, Verosky, Miyakawa, Knight, & D'Esposito, 2008). These findings suggest that neuroticism is associated with both heightened sensitivity to fear associations and enhanced fear conditioning during observational learning. Neuroticism was also associated with increased amygdala–hippocampus activation during reward learning, suggesting neuroticism is associated with an enhanced sensitivity to acquire conditioned associations to both punishment and reward. The authors suggested that this enhanced sensitivity may relate to the heightened baseline arousal seen in neuroticism, which provides an optimal arousal level for emotional learning. These findings further illustrate that a biological vulnerability toward heightened reactivity associated with neuroticism is not necessarily a sole precondition for pathology. One could argue that subsequent faster reactions to cues and enhanced conditional learning associated with neuroticism, as these results suggest, may have a positive, adaptive value. Rather, the adaptive versus maladaptive value of neuroticism may be more closely related to the interaction of biological and psychological factors presented earlier, such as overgeneralization of conditioned associations or rigid, inflexible, and context-indiscriminant response patterns (e.g., impulsivity, overgeneralization of fear, avoidance).

Taken together, the evidence suggests that both classical conditioning through direct experiences and observational or instructional learning play an important role in the acquisition of specific expressions of fear and anxiety, and neuroticism may potentiate these learned associations. Hence, if an individual high in neuroticism is confronted with learning experiences that create fear associations, these associations may develop into the foci of anxiety and, possibly, a disorder. For example, if an individual learns that physical illness is dangerous, either through witnessing his or her family's reaction whenever anyone becomes ill or parental enhancement of sick-role behaviors, the individual may focus anxiety on physical sensations that have been particularly salient, leading to the development of panic disorder or hypochondriasis. If the individual learns that disapproval from others has negative, even dangerous, consequences, social evaluation may become the focus of anxiety, leading to the development of social anxiety disorder. If the individual learns that having an aggressive thought is as reprehensible as acting on the thought (thought–action fusion), then intrusive, egodystonic thoughts may become the focus of anxiety and attempts to avoid or suppress these thoughts, leading to the development of obsessive-compulsive disorder (Barlow, 2002). Hence, general biological and psychological factors comprising neuroticism, when lined up with specific forms of learning experiences, may provide the optimum conditions for the development of certain specific emotional disorders.

Conclusions and Future Directions

Research reviewed in this article highlights the importance of gaining a better understanding of interactions between general biological and psychological vulnerabilities in the development of neuroticism. Although temperament is often considered a biological vulnerability, the literature suggests that a number of environmental variables contribute to the development of temperament and may moderate it over time. In an age of increased awareness of the dynamic nature of gene–environment interactions and the inherent difficulties related to drawing boundaries between genes and environment to explain phenotypic expression of emotional disorders, it is most likely the case that early environmental experiences substantially impact gene expression in the development of neuroticism.

In light of the public health costs associated with neuroticism, a discussion of the development of this temperament prompts consideration of its treatment. The literature reviewed in this article clearly indicates a transactional relationship between genetic and environmental inputs for personality, setting genetic contributions up as a predisposition but not a mandate. These studies beg the question of whether we can treat neuroticism directly, and evidence for the proposition has been reviewed elsewhere (Barlow et al., 2014).

However, even more intriguing is the possibility of intervention before a neurotic temperament fully develops. In fact, there is evidence to suggest that levels of behavioral inhibition at 2 years of age, which

has implications for emotional disorder onset in later childhood and adulthood (Kagan, 1989, 1994), can be predicted as early as 4 months of age from infant crying in response to novel stimuli (Moehler et al., 2008). Maternal diagnosis of a postpartum anxiety disorder has been shown to predict infant salivary cortisol reactivity in response to novel stimuli (Reck, Muller, Tietz, & Molher, 2013), suggesting that parental diagnostic status and infant physiological responses can be used to identify those at risk.

There is evidence from the animal literature suggesting strategies that may be useful in preventing development of this temperament; for example, newborn rats that were exposed to relatively novel environments for 3 min a day displayed less *behavioral inhibition* (defined as time spent in exploration after weaning) compared with newborn rats that stayed in their home cage (Tang, Reeb-Southerland, Romeo, & McEwen, 2012). These results were moderated by maternal rat HPA axis reactivity, suggesting that interventions may have to target both children and parents.

Along these lines, Rapee, Kennedy, Ingram, Edwards, and Sweeney (2005) developed a parent-focused intervention for preschool children identified as behaviorally inhibited with the purpose of reducing the frequency of current and future anxiety disorders. The intervention includes psychoeducation about the nature of anxiety, traditional cognitive-behavioral strategies, and training in behavior management techniques that prevent an overprotective parenting style. In two randomized controlled trials (Rapee et al., 2005, 2010), this program produced significant reductions in the frequency and severity of emerging anxiety disorders from preintervention to a postintervention follow-up assessment (12-month and 6-month follow-ups, respectively). More important, Rapee et al. also found that their early intervention program had an impact on behavioral inhibition, a temperament closely related to neuroticism (Barlow et al., 2014; Kagan, 1994). When administered in an intensive format with higher risk children, reductions in behavioral inhibition did occur compared with a control group that did not receive the treatment (Kennedy, Rapee, & Edwards, 2009). These differences among groups appeared to increase as time went by, suggesting that interventions directed at temperament might produce an increasing trajectory of change in this trait (Rapee et al., 2010).

In conclusion, existing research has begun to elucidate the biological and psychological factors that dynamically contribute to the development of neuroticism and, in turn, the relationship between neuroticism and the development of pathology, such as emotional disorders. These findings suggest the possibility of identifying both potential targets for intervention and possibilities for prevention. Future studies are needed to explore whether interventions developed to target vulnerabilities specifically (e.g., interventions that reduce or aid in the regulation of heightened physiological reactivity; interventions that directly address perceptions of uncontrollability/unpredictability) can affect the development of neuroticism and, ultimately, emotional disorders.

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Notes

1. Drawing distinctions between temperament and personality on the basis of their stability (temperament as an unfolding developmental process that eventually solidifies into one's enduring personality) may be artificial (Rothbart, 1999), as recent research indicates that personality may be more malleable than originally believed (McCrae & Costa, 1994). Given the lack of empirical support for differentiating between these constructs, the terms personality and temperament are used interchangeably in this article, and we take advantage of the vast literatures related to both areas of research.
2. IEGs are genes whose transcription is activated by extracellular stimuli rapidly (within minutes) and transiently (Sheng & Greenberg, 1990). IEGs encode transcription factors that influence gene expression and neuronal plasticity, leading to long-term alterations in neuronal functioning. Thus, the expression of IEGs through neuronal kindling can have long-lasting effects on brain organization and functioning, resulting in enduring phenotypic changes in response to stimuli (Pérez-Cadahía, Drobic, & Davie, 2011).

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