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Improving the Prediction of Risk for Anxiety Development in Temperamentally Fearful Children

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Abstract
Pediatric anxiety disorders are among the most common disorders in children and adolescents, resulting in both short-term and long-term negative consequences across social, academic, and other domains. Early fearful temperament has emerged as a strong predictor of anxiety development in childhood; however, not all fearful children become anxious. The current article summarizes theory and evidence for heterogeneity among children identified as temperamentally fearful and trajectories of risk for anxiety. The findings presented in this article reveal that identification of subgroups of fearful temperament improves prediction of who is at risk for developing anxiety problems.

Keywords
fearful temperament, anxiety development, psychophysiology

Pediatric anxiety risk has been widely studied because of the impact anxiety symptoms have on social and academic spheres across development. These symptoms have both short-term and long-term effects on a child's functioning, and when anxiety persists across development, it increases risk for depression, substance use, and other adjustment problems in adulthood (Pine, Cohen, Gurley, Brook, & Ma, 1998). Children with anxiety symptoms tend to avoid social interactions with peers, are perceived as less socially competent, have fewer friendships, and are more likely to be bullied by peers (Rubin, Coplan, & Bowker, 2009). Anxiety also contributes to difficulty with adjusting to school transitions and overall academic performance (Buss et al., 2013; Wood, 2006). Thus, there is critical need to (a) identify children who are at greatest risk for adjustment difficulties and pediatric anxiety and (b) understand how anxiety develops across childhood into adolescence.

Who Is at Risk for Developing Anxiety Problems?

The etiology and developmental course of anxiety symptoms is complex, reflecting biological, psychological, and social processes. Researchers have focused on early risks, particularly fearful temperamental dispositions, that help to identify children who might develop pediatric anxiety. Across multiple studies, extreme fearful temperament, identified in infancy, has emerged as the best early dispositional predictor of anxiety and, specifically, social anxiety (Chronis-Tuscano et al., 2009).

Fearful temperament, most commonly studied as behavioral inhibition, has been linked in study after study to the development of anxiety symptoms. Behavioral inhibition is the tendency to withdraw from, avoid, or react fearfully to novel situations (Kagan & Fox, 2006). These behavioral reactions correspond to physiological reactions (e.g., increased heart rate) that indicate fearful emotions in response to novel situations. When inhibition remains stable throughout infancy and into childhood, it poses risks for social anxiety symptoms (Chronis-Tuscano et al., 2009).

Not all work examining early risk for anxiety development has focused on fearful temperament specifically, and there are other factors that contribute

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to the development of anxiety for fearful children (e.g., parenting, peers). Specifically, social withdrawal has been linked to difficulties in interacting with peers, developing relationships, and adjusting and succeeding in school (Rubin et al., 2009). Several overlapping constructs (social reticence, shyness, anxious solitude) reflecting some form of social withdrawal or social avoidance (Coplan & Rubin, 2010) have also been linked to development of anxiety problems across development. Moreover, these forms of social withdrawal are often preceded by fearful temperament in infancy. Fearful children tend to display *social reticence*—characterized by frequent hovering, onlooking, and anxious behavior in peer interactions—which can interfere with adaptive social engagement and result in anxiety (Degnan et al., 2014). For instance, trajectories of high, stable social reticence from age 2 to age 5 predict more internalizing (e.g., anxiety) problems at age 5 as reported by mothers (Degnan et al., 2014). This work demonstrates that the stability of these traits and behavior patterns places children at increased risk for maladaptive trajectories. In a related line of work, Gazelle has identified a pattern of anxious solitude whereby children are socially withdrawn with familiar peers (Gazelle, 2008). Consistent with the hypothesis that this would be a more extreme presentation of social withdrawal, this anxious solitude has also been linked to increased risk for social anxiety disorder symptoms (Gazelle, Workman, & Allan, 2010).

Heterogeneity and Identification of Subgroups

There is considerable heterogeneity in the identification of risk, across developmental trajectories, and in outcomes. Although stable fearful temperament is a robust predictor of risk for anxiety, not all fearful children become socially withdrawn or develop anxiety symptoms. This heterogeneity may be the result of how fearful behavior is measured. In the case of fearful temperament, one could consider its motivational aspects (e.g., withdrawal, avoidance), communicative/distress behaviors (e.g., facial expressions, crying), behavioral reactions (e.g., flight or freeze), or social wariness (e.g., shyness, social reticence, social withdrawal). Therefore, we cannot assume that any two groups of temperamentally fearful children—for example, one identified based on distress behaviors and the other identified based on avoidance behaviors—are homogeneous.

Although individuals with fearful/anxious temperaments are often characterized using one or more related behaviors or indices (e.g., decreased vocalizations, freezing, avoidance, withdrawal from novelty, elevated stress reactivity), not all fearful individuals show variation in all of these. Using a nonhuman primate model, Shackman and colleagues demonstrated both a core set of common biological substrates that are shared by all individuals in the spectrum of fearful and anxious temperament and, also, selective substrates that were uniquely associated with different dimensions (Shackman et al., 2013). These findings have implications for distinguishing different subgroups of fearful/anxious individuals, suggesting that there may be different groups of temperamentally fearful children at differential risk. So, it is important to understand this heterogeneity. What are its implications? How can we capitalize on these differences to better identify, and understand, children on developmental trajectories of risk?

To address these questions, we have concentrated on the role of the eliciting context in the identification of which fearful children are at greatest risk for anxiety. Individual differences in fearful temperament are most often operationalized by averaging behavioral measures across situations, because this method is believed to capture the consistency of behavior across situations. However, upon closer examination of the correlations across situations, the behavioral indicators of inhibition are only modestly correlated and low in many cases (Buss, Davidson, Kalin, & Goldsmith, 2004; Garcia-Coll, Kagan, & Reznick, 1984), suggesting that the same behaviors may not be elicited across different situations. We have argued that simply averaging behavior across multiple situations may obscure meaningful individual differences and may cause us to miss children who show extreme fear only in specific contexts (Buss et al., 2004). This is likely because situations used to elicit these fearful behaviors differ in their incentive properties (e.g., novelty, level of threat, controllability).

This idea has been recognized in the social psychology literature as the distinction between strong and weak situations, where strong situations are those that result in nearly uniform reactions and therefore low variability across individuals, whereas weak situations enhance the detection of individual differences by weakening the "potency" of the situation (Mischel, Mendoza-Denton, & Shoda, 2002). For instance, in the anxiety-conditioning literature, Grillon and colleagues have demonstrated that high-threat (i.e., strong) situations elicit a more uniform fear response across anxious patients and control participants, whereas low-threat (i.e., weak) situations elicit a fear response only in the anxious participants (Lissek, Pine, & Grillon, 2006). Moreover, this work also demonstrated that it may be the likelihood that the situation elicits a response that is critical (Grillon, Baas, Lissek, Smith, & Milstein, 2004).

Consistent with these ideas, a compelling nonhuman primate model of anxious temperament guided our initial work. Kalin focused on a tendency of some animals to freeze in situations where freezing was not the typical or

adaptive response (Kalin, 1993). This maladaptive behavior reflects the dysregulation of the animal's fear behavior because the animal's behavior does not match the incentive properties of the situation. This research served as a model for our hypothesis that dysregulation of fear behaviors across contexts may have negative consequences for temperamentally fearful children. Thus, we hypothesized that focusing on fear responses in low-threat (i.e., weak) situations would yield a more homogeneous group of fearful children who would be empirically distinct from behaviorally inhibited children.

As an initial test of this hypothesis, we exposed 24-month-old children to three different stranger-approach situations—one in which the child was playing with toys on the floor, one in which the child was in a high chair eating a snack, and one in which the child was in a high chair while cardiac physiology was being recorded. For most children, the stranger approach in a free-play context was the least threatening—as measured by amount of fear behaviors (e.g., freezing) observed (Buss et al., 2004). However, there were still a number of children who displayed long durations of freezing in this lower-threat context (where coping resources were readily available), and this pattern was associated with greater stress reactivity. Thus, freezing in this situation was argued to be less adaptive and dysregulated because children failed to take advantage of coping resources.

As a next step, we designed a more extensive protocol involving six novel situations designed to vary in the putative level (low, moderate, high) and type (social vs. nonsocial) of threat (Buss, 2011). In this protocol, 24-month-olds were exposed to a puppet show and a friendly clown in two episodes (in which the child was invited to play with toys), two stranger situations (a "conversation" with a male stranger and a female stranger "working" in the corner), a remote-controlled robot, and a large stuffed spider (placed on top of a remote controlled vehicle) that approaches the child. There were predictable differences in fear and approach behaviors across the different situations (Fig. 1), such that the clown and puppet show resulted in the lowest amount of fear behavior, the stranger episodes resulted in moderate amounts of fear, and the robot and spider resulted in the highest amount of fear. We examined individual patterns of fear behavior across the situations ordered from lowest to highest threat. The average pattern was an increasing slope from lower- to higher-threat situations. However, there was a range of individual slopes indicating that for a subgroup of children, there was a flat slope with high fear across all situations. Latent profiles (Fig. 2) highlight the distinction between profiles in the low-threat situations because these two profiles were indistinguishable in the high-threat situations. Importantly, we found that children who displayed this pattern of high fearfulness across both low-threat and high-threat situations were more likely to be socially withdrawn in preschool and at entry to kindergarten (Buss, 2011), even compared to other groups of fearful children. In addition, these children were stable in this behavioral pattern of high fear in low-threat situations; were more likely to show social reticence with unfamiliar peers than were nonfearful children; and were more likely to develop social anxiety symptoms in early childhood than were other shy children in kindergarten (Buss et al., 2013).

What Accounts for This Pattern of Fearful Behavior?

Our current work has been focused on understanding the underlying mechanisms that account for this pattern of high fear behavior in low-threat situations. Is this pattern of high fear under low threat the result of increased fear reactivity, difficulty with regulating fear, or (most likely) both of these processes?

Kagan has theorized that a proximal cause of extreme fearful temperament is a biological diathesis that gives rise to a pattern of fearful and anxious behavior (Kagan, 1994). Research has supported this by showing that dysregulation of physiological systems is common in children with internalizing (e.g., anxiety) disorders (Bauer, Quas, & Boyce, 2002), and anxiety disorders are increasingly recognized as neurodevelopmental in etiology (Guyer,

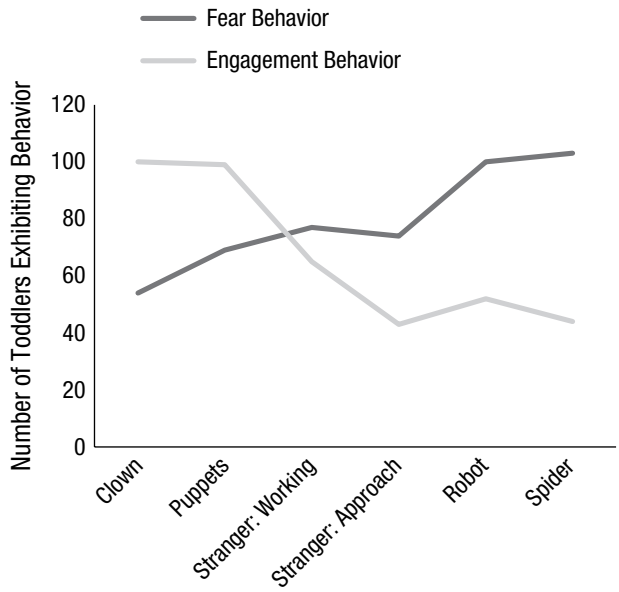

Fig. 1. Number of toddlers displaying fear and engagement behavior across episodes in Buss (2011). Adapted from "Which Fearful Toddlers Should We Worry About? Context, Fear Regulation, and Anxiety Risk," *Developmental Psychology, 47*(3), p. 812. doi:10.1037/a0023227. Copyright 2011 by the American Psychological Association. Adapted with permission.

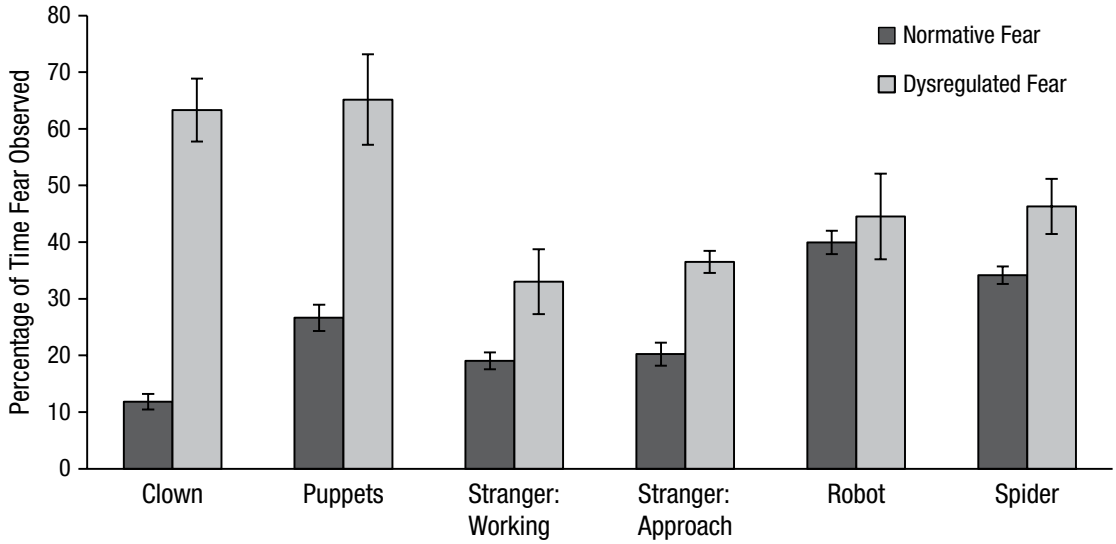

Fig. 2. Patterns of fear across episodes for two latent profiles drawn from Buss (2011). Error bars show standard errors. Adapted from "Which Fearful Toddlers Should We Worry About? Context, Fear Regulation, and Anxiety Risk," *Developmental Psychology, 47*(3), p. 812. doi:10.1037/a0023227. Copyright 2011 by the American Psychological Association. Adapted with permission.

Masten, & Pine, 2013). Multiple components have been implicated in the neural circuitry of fearful temperament and anxiety, such as the amygdala, cingulate cortex, prefrontal cortex, and autonomic nervous and neuroendocrine systems (Clauss, Avery, & Blackford, 2015; Guyer et al., 2013).

The patterns of reactivity in neurophysiological systems are shared across temperamental fearfulness and pediatric anxiety disorders, suggesting a common pathophysiology (Guyer et al., 2013). However, there have also been mixed findings in the association between fearful and/or anxious behavior and biological indices. Consistent with findings reviewed above (Shackman et al., 2013), we believe that this suggests heterogeneity and that the identification of subgroups may improve prediction of who is at risk and the identification of the underlying processes that account for the development of anxiety in temperamentally fearful children.

We have emerging evidence for a distinct pattern of behavioral and biological correlates of the dysregulated fear profile, reflecting both reactive and regulatory processes. Dysregulated fear is associated with greater stress reactivity—specifically, higher basal cortisol and faster cardiac pre-ejection period (a measure of sympathetic reactivity; Buss et al., 2004). The parasympathetic branch of the autonomic nervous system plays an important role in physiological regulation of stress (Porges, 2007), and over the past two decades there has been a wealth of studies examining markers of this process using cardiac respiratory sinus arrhythmia (RSA). Low baseline levels of RSA and failure to regulate RSA (i.e., suppress RSA in response to task demands) have been associated with emotion-regulation difficulty (Buss, Goldsmith, & Davidson, 2005), trajectories of social wariness (Hastings, Kahle, & Nuselovici, 2014), and anxiety symptoms (Licht, de Geus, van Dyck, & Penninx, 2009). Consistent with these findings, at 24 months, dysregulated fear is associated with a dynamic pattern of RSA consistent with poor regulation (Buss, Davis, Ram, & Coccia, 2015).

Additional evidence for difficulty with regulation among children with dysregulated fear comes from our work examining neural mechanisms derived from EEG recordings. We have found that children with a dysregulated fear profile show greater neural activity reflecting increased performance monitoring—common in anxious individuals (Brooker & Buss, 2014). These children also show greater coupling between frequency bands in baseline EEG (Phelps, Brooker, & Buss, 2016) believed to reflect overcontrol of behavior.

Finally, Kalin and colleagues have suggested that children with stable anxious temperaments fail to learn from their environment and cannot differentiate safe from threatening environments/situations. Using a nonhuman primate model, they demonstrated that animals with stable amygdala metabolism were more likely to show an anxious temperament, and these anxious animals had reduced gene expression in the amygdala suggesting reduced neuroplasticity (Fox et al., 2012), which could account for a failure to learn from the environment. Consistent with this interpretation, anxious children (Roy et al., 2008) show spontaneous biases to threat stimuli in their environments. Behaviorally

inhibited children show a similar bias toward threat, and the magnitude of this bias helps sustain a developmental link between early inhibition and later anxiety (Pérez-Edgar et al., 2011). However, there is inconsistency in the pattern of findings whereby not all temperamentally fearful or anxious children show this bias. Consistent with our hypothesis that children with dysregulated fear are a unique subgroup of temperamentally fearful children, we found that these children were more likely to show a bias away from threat (Morales, Pérez-Edgar, & Buss, 2014).

Although we still lack a complete understanding of the biological-behavioral link, it is critical to examine biological mechanisms (i.e., biomarkers) that inform developmental processes because these markers often indicate differences that are not always observed. For instance, Xu and colleagues found that although all shy children showed the predicted heart-rate changes in response to a stressor, not all groups showed inhibited behavior (Xu, Farver, Yu, & Zhang, 2009). Consistent with our findings, this heterogeneity highlights the importance of examining different subgroups, but it also raises important issue of whether it is the underlying physiology/neurobiology or the behavior that is important in determining risk for anxiety.

Conclusions and Future Directions

In this article, we have summarized theory and research demonstrating heterogeneity in risk for anxiety among children characterized by extreme fearful temperament. This literature suggests that there are different subgroups of fearful children—characterized by a partially unique set of biomarkers and mechanisms—who may be at differential risk for anxiety development. Identification of these subgroups, unique mechanisms, and risk trajectories will have important implications for early intervention in the prevention of anxiety problems. In fact, this conceptual framework and the empirical findings supporting the heterogeneity in temperament and etiology of anxiety symptoms have already been applied to cutting-edge interventions to treat and prevent anxiety in children (Chronis-Tuscano et al., 2015; Rapee, Kennedy, Ingram, Edwards, & Sweeney, 2010). These types of programs demonstrate the effectiveness of temperamentally based treatment approaches.

Although this work highlights the importance of examining who may be at particular risk for development of anxiety, research is still needed to (a) understand variation in trajectories for fearful children, (b) identify the underlying mechanisms that account for these behavioral differences, (c) examine environmental factors (e.g., parents, peers, cultural variation) that influence the trajectories toward or away from risk, and (d) determine if these differences between subgroups translate to meaningful, real-world differences in outcomes.

Recommended Reading

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