Psychobiological Processes in the Development of Behavioral Inhibition

Kristin A. Buss and Jin Qu

Abstract Despite robust prediction from early behavioral inhibition to anxiety development, evidence is accumulating for heterogeneity among children identified as behaviorally inhibited. In this chapter, we examine how behavioral inhibition is associated with a range of psychophysiological markers to better understand this heterogeneity. We suggest that these measures are not just correlated with behavioral inhibition but are markers of underlying processes that help to characterize which children are at highest risk for anxiety, thereby reducing heterogeneity. We organize the literature by discussing physiological markers as indexing reactivity and regulation, consistent with a temperament framework, and cover a wide range of physiological measures linked to behavioral inhibition and risk for anxiety, including electrodermal activity, cortisol, and EEG asymmetry, respiratory sinus arrhythmia, EEG delta-beta coupling, and event-related potentials. The findings presented herein support the notion that these physiological markers index mechanisms that contribute to children's behavioral manifestation of behavioral inhibition and may exacerbate the risk for inhibited children to remain on the trajectory of developing anxiety symptoms.

Psychobiological Processes in the Development of Behavioral Inhibition

Behavioral inhibition—or extreme fearful temperament more broadly defined—is the tendency to avoid and withdraw to novel situations, often while showing fearful reactions (García Coll, Kagan, & Reznick, 1984; Kagan & Fox, 2006). Behavioral inhibition is among the strongest early predictors of anxiety symptom development, specifically social anxiety (Beesdo, Knappe, & Pine, 2009). When inhibition is stable throughout the childhood (Chronis-Tuscano et al., 2009; Essex, Klein, Slattery, Goldsmith, & Kalin, 2010), and when inhibition is displayed more prominently in

K. A. Buss (✉) · J. Qu
Department of Psychology, Clarion University, Clarion, PA, USA
e-mail: kab37@psu.edu; jqu@clarion.edu

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certain contexts (Buss, 2011; Buss et al., 2013), this increases the risk for social anxiety symptoms.

Perhaps due to the robust and consistent nature of the findings in the literature, there is an implicit assumption that temperamentally fearful children are a homogeneous group. However, most inhibited toddlers, despite being at increased risk for anxiety development, ultimately mature to become healthy children (Pine, Helfinstein, Bar-Haim, Nelson, & Fox, 2009). Two related questions emerge in attempts to explain these findings: (1) Which children are the ones that we should worry about? That is, what are the unique *characteristics* that are associated with risk for social anxiety development in inhibited children? (2) What *factors or processes* are associated with increased risk for social anxiety? Differences in outcome may have roots in early heterogeneity among temperamentally fearful children.

As the first question suggests, not all fearful/inhibited children are the same, and perhaps only a certain type of inhibited child develops social anxiety. This has been the focus of our work as well as others using human and nonhuman models (see the chapter "Behavioral Inhibition in Nonhuman Primates: The Elephant in the Room" by Capitanio and the chapter "Behavioral Inhibition in Rodents: A Model to Study Causes and Health Consequences of Temperament" by Cavigelli). In addressing the issue of heterogeneity, we argue that fearful temperament needs to be measured dynamically across situations and development because children's reactions to or interpretations of situations (as threatening or not) will determine more precisely whether behavior is, or will be, maladaptive. We characterized extreme fearful behavior in toddlers across a series of novel laboratory situations ranging from low to high threat (Buss, 2011) as an index of fear sensitivity (Buss, Davis, Ram, & Coccia, 2018). By examining how fear changes across these situations, we have been able to quantify a dimension of fear regulation ranging from *well-regulated fear* (fear increases in expected ways with increases in putative threat) to *dysregulated fear* (fear is higher than expected to putatively lower threat situations because these situations are reacted to or interpreted as potential threats). Had we not assessed fear across a range of situations (especially those low in putative threat), we would have missed identification of these children altogether—they are indistinguishable from other inhibited children in higher threat contexts. Importantly, dysregulated fear (DF) pattern at age 2 predicts reported and observed social withdrawal behavior at 3, 4, and 5 years (Buss, 2011) and social anxiety disorder symptoms at age 6 and in early adolescence (Buss et al., 2013; Buss et al., 2018).

What accounts for this heterogeneity? Other factors or characteristics could differentiate which fearful children are at highest risk, reflecting the underlying processes that account for the fearful, inhibited, and anxious behavior. From a temperament perspective, the processes that account for behavioral differences include both reactive and regulatory processes (Rothbart, 2011). We, and others, argue that examining physiological processes may help in elucidating the underlying processes that link behavioral inhibition to social anxiety symptom development (see the chapter "The Neurobiology of Behavioral Inhibition as a Developmental Mechanism" by Blackford et al.) and may help tease apart inhibited behavior that

does not confer risk for social anxiety (i.e., the false-positive cases of inhibition) from the at-risk cases.

Numerous studies, some of which will be summarized in this chapter, have documented dysregulated physiological measures and systems associated with fearful and anxious behavior (Davidson, Jackson, & Kalin, 2000; Fox, Henderson, Marshall, Nichols, & Ghera, 2005; Rothbart, 2011). Moreover, greater attention has been paid to integrating across biological and psychological domains in explicating the development of anxiety across development (Bauer, Quas, & Boyce, 2002). In the sections that follow, we review the evidence for the links between different physiological measures and behavioral inhibition. This review is not exhaustive but rather will highlight the underlying processes and mechanisms we believe are associated with the behavior pattern of inhibited children at highest risk for difficulties with social anxiety. In our read of the literature over the past 25 years, we believe there are a few key processes that are highlighted in the work examining links among physiology, inhibited behavior, and risk for anxiety development. These include, but are not limited to, the role of (stress) reactivity, regulation or dysregulation in context, and executive processes. We will conclude with our view of what these findings to date mean and recommendations for future directions.

Behavioral Inhibition and Increased Reactivity

Kagan (1994) suggested that behaviorally inhibited children have lower threshold of sensitivity in the amygdala that give rise to the inhibition, fear, and withdrawal (see the chapter "The History and Theory of Behavioral Inhibition" by Kagan). Decades of work has examined physiological markers of this hypothesis including increases in heart rate (Degnan & Fox, 2007) and other SNS-mediated markers, stress physiology such as cortisol, and examination of neural mechanisms that may be markers of fear and withdrawal behavior (see the chapter "The Neural Mechanisms of Behavioral Inhibition" by Jarcho and Guyer). We review some of this work by focusing on three measures: electrodermal activity (EDA), cortisol, and EEG asymmetry and coherence.

Electrodermal Activity

Electrodermal activity (EDA) is caused by activity in sweat glands when activated by the sympathetic nervous system (SNS) during times of physical or psychological stress (El-Sheikh et al., 2009). This electrodermal activity is accompanied by increased oxygenation in the body and increased heart rate to prepare the body for action (Boucsein, 2012). However, there are individual differences in terms of how easily the SNS system can be activated and the length and intensity of SNS activation (Fowles, Kochanka, & Murray, 2000). Generally, elevation in SNS can be

considered adaptive as the body mobilizes its resources to cope with environmental challenges (El-Sheikh et al., 2009). However, prolonged SNS reactivity is maladaptive and can produce negative health consequences in the body (McEwen, 1998; see the chapter "Behavioral Inhibition in Rodents: A Model to Study Causes and Health Consequences of Temperament" by Cavigelli). Skin conductance has been used to examine the relation between children's stress reactivity and internalizing symptoms, setting the foundation for studies specifically focused on anxiety risk and behavioral inhibition.

Most of the skin-conductance literature has focused on adult samples. However, there are a few notable studies examining skin-conductance levels in relation to behavioral inhibition in children. Toddlers who were high on behavioral inhibition showed higher skin-conductance levels while at rest compared to children who were low on behavioral inhibition (Scarpa, Raine, Venables, & Mednick, 1997). Additionally, a handful of studies also examined EDA with additional moderators such as parenting quality or other physiological measures.

Temperamentally fearful preschoolers showed higher EDA to the fearful-eliciting stimulus when they had lower parent-child relationship quality (Gilissen, Koolstra, van Ijzendoorn, Bakermans-Kranenburg, & van Veer, 2007). Thus, poor parent-child relationship quality is one context in which we see evidence for a link between stress reactivity and fearful temperament, because not all fearful children showed higher EDA. EDA has also been examined together with RSA to form parasympathetic nervous system (PNS)-SNS activation profiles in predicting anxiety symptoms (El-Sheikh, Keiley, Erath, & Dyer, 2013). In contrast to the findings with behavioral inhibition, children who exhibited lower EDA reactivity and lower RSA reactivity were at highest risk of developing anxiety symptoms, whereas children who showed higher RSA and lower EDA at baseline demonstrated decreased anxiety over time.

Furthermore, these general findings also differed based on child gender and levels of family conflict (El-Sheikh et al., 2013). Specifically, girls from higher conflict homes who had both low baseline RSA and EDA had higher and increasing levels of anxiety over time, whereas boys showed the opposite pattern such that their anxiety started out high at age 8 but declined over time. Behavioral inhibition has been shown to correlate with higher EDA levels, although other work examining anxiety symptoms demonstrates the opposite pattern. One consistent component across these studies is evidence of environmental factors, such as parenting, and other physiological markers that may moderate these effects.

In sum, children with higher behavioral inhibition and/or anxious traits also demonstrate higher EDA consistent with the stress-response hypothesis that EDA will be elevated in stressful situations, but only under certain environmental contexts such as parenting. These findings are consistent with our previous work on context effects (Buss, 2011). Moreover, the interactions with other physiological markers suggest heterogeneity, such that not all fearful children will display an elevated stress response. In this case, it may be that the response is potentiated only when coupled with difficulty regulating—as marked by poorer physiological regulation (see RSA section later in this chapter).

Cortisol

Cortisol is the main glucocorticoid of the hypothalamic-pituitary-adrenocortical (HPA) system and it reflects elevated activity in the limbic system (amygdala and bed nucleus of the stria terminalis) (Kalin, Shelton, Fox, Oakes, & Davidson, 2005; Schwartz, Wright, Shin, Kagan, & Rauch, 2003). This neuroendocrine response system is regulated by the central nucleus of the amygdala (Fox et al., 2005). Elevations in cortisol are part of the cascade of physiological changes that occur under stress, increasing glucose available to the muscles for "fight or flight" response (Doom & Gunnar, 2013).

Like other physiological processes, activation of the HPA axis is sensitive to a variety of psychological and social stressors. Moreover, prolonged elevation of cortisol may pose cardiovascular-related health risks such as elevation of blood pressure, insulin resistance, and truncal obesity (Whitworth, Williamson, Mangos, & Kelly, 2005). In addition, the persistent elevation of cortisol may be associated with smaller volume in the hippocampus, a brain region implicated in memory, motivation, and emotion (Pagliaccio et al., 2014). Prolonged elevations of cortisol levels may lower the threshold to trigger children's next cortisol activation and also interfere with recovery from with stress (Buss, Davis, & Kiel, 2011). Therefore, it is important to examine for whom elevations in cortisol are most likely and under what circumstances elevations occur.

Children with high baseline cortisol levels displayed social withdrawal and social reticence, a marker of behavioral inhibition, at age 4 (Pérez-Edgar, Schmidt, Henderson, Schulkin, & Fox, 2008). This finding was the strongest for boys who also displayed higher levels of negative affect as infants. These data may suggest a pathway supporting the larger finding that boys high in behavioral inhibition go on to display more anxiety than their equally inhibited female peers (Fox, Snidman, Haas, Degnan, & Kagan, 2015). Furthermore, there seems to be a bidirectional effect between behavioral inhibition and cortisol levels across development.

Higher cortisol levels at 4.5 years predicted mother and teacher reports of social wariness in kindergarten (Smider et al., 2002). In a follow-up study with the same longitudinal sample, cortisol levels at 4.5 years were positively associated with chronic behavioral inhibition assessed from grade 1 through grade 9 (Essex et al., 2010). In another study examining change in cortisol levels across the Trier Social Stress test for Children (TSST-C), behavioral inhibition at age 7 was positively associated with higher baseline cortisol (measured as AUC_g, area under the curve ground) and cortisol reactivity (indexed by AUC_i, area under the curve increase) at age 9 (Mackrell et al., 2014). Thus, stability in behavioral inhibition may be, in part, accounted for by consistency of the HPA stress response, suggesting that stress reactivity may also contribute to identification of the most vulnerable inhibited children.

The associations between elevated cortisol levels and fear behaviors have been well documented in the nonhuman primate literature (Dettmer, Novak, Suomi, & Meyer, 2012; Shackman et al., 2013). Using a rhesus macaque model, monkeys

who exhibited higher baseline cortisol exhibited more freezing behavior compared to those who exhibited lower baseline cortisol levels (Kalin, 1993). Moreover, Shackman et al. (2013) distinguished the brain regions that predicted elevated cortisol levels, freezing behavior, and vocalization indicating that there are heterogeneous dimensions of anxious temperament in the animal model. This is consistent with our model (Buss & Kiel, 2013) and data with toddlers demonstrating heterogeneity across fearful temperament profiles and emerging evidence for an accompanying unique pattern of physiology (Buss, 2011; Buss et al., 2013; Buss, Davis, et al., 2018).

Variation in environmental contexts and transitions may highlight the association between temperament and stress reactivity. For instance, some children may experience elevated stress during the transition to school (Russ et al., 2012; Tarullo, Mliner, & Gunnar, 2011). Specifically, Tarullo et al. (2011) found that cortisol levels for highly inhibited children remained elevated across the school year, compared to cortisol levels in highly exuberant children, that is, children who are high on positive reactivity and approach (Fox, 1991). Consistent with the findings, children who were classified as "inhibited" at 14 months and whose mothers were diagnosed with social phobia displayed higher afternoon cortisol collected 1 month before starting school, the first week at school, and near the end of the first term (Russ et al., 2012).

Other environmental factors may also contribute to the pattern of stress reactivity observed. For instance, for behaviorally inhibited children, having more friends and being more dominant and popular were actually associated with increasing cortisol levels over the school years (Tarullo et al., 2011). Therefore, children with behavioral inhibition are more likely to show prolonged cortisol elevation during the transition to school and to experience elevated stress associated with social interactions. These findings illustrate the importance of examining the interactions among children's inhibited temperament and the social environment to predict their physiological reactivity. The positive peer context for exuberant children may not be the equivalent positive peer context for children with behavioral inhibition.

In addition to the cortisol stress response, cortisol "regulation," or stress recovery, has also been examined in relation to behavioral inhibition. Cortisol regulation, indexed by the extent and speed of recovery after a social stressor, may buffer children who are high on shyness from demonstrating high solitary/reticent behaviors (Davis & Buss, 2012). In a sample of 6-year-olds, parent-reported shyness was positively associated with shyness/reticence and solitary passive play behavior only when children had low levels of cortisol recovery (Davis & Buss, 2012). Thus, the ability to regulate cortisol levels may be adaptive such that recovery from a cortisol stress response for inhibited children may support social competence.

In addition, parenting behaviors play an important role for inhibited children's elevation in cortisol. Specifically, maternal overprotection may prevent the opportunities for children to be more autonomous, which in turn exacerbates children's behavioral inhibition behaviors (Hutt, Buss, & Kiel, 2013). Higher levels of caregiver protective behaviors predicted higher levels of cortisol reactivity (indexed by an increase of cortisol levels from the baseline) above and beyond toddler's observed fear and sadness (Hutt et al., 2013). Caregivers' activity also mediated toddlers' fear

and sadness and their cortisol reactivity, such that mothers who not only were able to predict their children's fear, but also protected their children from getting exposed to the external stimulus, had children with higher behavioral inhibition (Hutt et al., 2013). Similarly, mothers who have an insecure attachment with their children may be overly intrusive and encourage their children to try fearful tasks without paying attention to children's needs. Having a secure attachment may buffer children with fearful temperament from experiencing elevated cortisol (Nachmias, Gunnar, Mangelsdorf, Parritz, & Buss, 1996). Together these examples highlight the important role that the caregiving environment plays on stress reactivity for children with behavioral inhibition.

In sum, elevated cortisol level may serve as a stress-reactivity marker for behaviorally inhibited children. The impact of peer, school, and the caregiving contexts suggests that children's levels of stress reactivity are malleable to environmental influences and can be regulated to a certain degree (Davis & Buss, 2012; Hutt et al., 2013). Even though EDA and elevated cortisol have been found to be physiological markers for behavioral inhibition, the findings always need to be considered in specific environmental contexts. Therefore, whether or not individual differences in stress reactivity help address the question of heterogeneity and aid in the identification of which children are at greatest risk is still an open question.

Neural Correlates: EEG Asymmetry

The anterior regions of both hemispheres may be lateralized for the behavioral/motivational systems involved in approach and withdrawal behaviors (Davidson, 1988; Fox, 1991). For example, a recent study of 9- to 12-year-old children (Taber-Thomas, Galinsky, Morales, Thai, & Pérez-Edgar, in prep) suggests that EEG asymmetry patterns reflect functional connectivity patterns in frontolimbic networks. The two sides of the frontal cortex may be associated with approach or withdrawal tendencies. The left frontal area is associated with approach behaviors that can be measured via positive emotions and other motor behaviors (Fox & Davidson, 1984). The right fontal area is associated with behaviors that are characterized by withdrawing from a novel or a stressful stimulus, and this withdrawal tendency is usually assessed via measuring autonomic reactivity and expressions of negative affect (Fox & Davidson, 1984), with the exception of anger, which is considered an approach emotion.

Individuals with behavioral inhibition usually demonstrate right frontal EEG asymmetry (Degnan & Fox, 2007). This pattern is evident as early as infancy (Calkins, Fox, & Marshall, 1996) and among young children (Fox, Henderson, Rubin, Calkins, & Schmidt, 2001). Right fontal asymmetry has also been found in children who demonstrated anxious behaviors during social interactions (Fox et al., 1995; Henderson, Fox, & Rubin, 2001).

In addition, the presence of right frontal EEG asymmetry increases the likelihood that behaviorally inhibited children will demonstrate poor social behavior

(Henderson et al., 2001). Furthermore, frontal EEG asymmetry is also associated with the stability of behavioral inhibition. Stability of behavioral inhibition from age 3 to age 10 was only observed when children also showed stable right frontal asymmetry from age 3 to age 10 (Davidson & Rickman, 1999), suggesting that right frontal EEG asymmetry serves as a physiological marker of behavioral inhibition traits in children.

In the adult literature, right frontal EEG asymmetry has been associated with negative affect, behavioral withdrawal, behavioral inhibition, anxiety, and depression (Harmon-Jones, Gable, & Peterson, 2010). For instance, attention bias to threat—a correlate of behavioral inhibition—has been associated with increased right frontal EEG asymmetry in response to stress (Pérez-Edgar, Kujawa, Nelson, Cole, & Zapp, 2013). In a fear context, decreased alpha power (increased cortical activity) in the right fontal (F4) site was correlated with higher scores on a behavioral inhibition measure (Balconi & Mazza, 2010). Similar patterns were also found in the context of anger and surprise (Balconi & Mazza, 2010). On the other hand, individuals characterized by the behavioral approach system had greater left (vs. right) side frontal cortical activity (Amodio, Master, Yee, & Taylor, 2008). Therefore, findings from the adult literature are consistent with those reported from child literature.

In sum, right frontal EEG asymmetry is generally associated with higher behavioral inhibition and anxious traits across development; thus, it is, at minimum, an important neural correlate of behavioral inhibition behaviors. However, we suggest that the pattern of results is robust enough to suggest that right frontal asymmetry is a marker of behavioral inhibition and could be used as an additional measure to identify these children. Considering that the association is stable in both childhood and adulthood, right frontal EEG asymmetry may also be an underlying mechanism supporting the behavioral manifestation of inhibited behaviors. Thus, the presence of this pattern of neural activity would help to increase homogeneity of children identified as behaviorally inhibited.

Behavioral Inhibition and Self–Regulation

In the previous section, we summarized data across a few physiological systems that suggests behavioral inhibition is associated with, or marked by, an underlying reactivity bias. In particular, children evidence an increase in cortisol, EDA, and right frontal EEG asymmetry. This is consistent with the theoretical explanations of inhibited behavior put forth by Kagan and with underlying neural mechanisms of fear and anxiety. However, reactive processes may not explain all of the differences that are observed at the phenotypic level. Moreover, these reactivity processes do not operate in isolation. In this section, we will briefly discuss physiological systems that demonstrate that regulatory and specific executive processes are also implicated in inhibited and anxious behavior across development.

Parasympathetic Vagal Tone Via Respiratory Sinus Arrhythmia (RSA)

Vagal tone, an index of heart rate variability, is usually measured via respiratory sinus arrhythmia (RSA). RSA refers to the high frequency variability in heart rate that occurs at the frequency of spontaneous respiration (Calkins, Graziano, Berdan, Keane, & Degnan, 2008; Porges, 1996). The vagus nerve is the 10th cranial nerve, has efferent connections to the heart, and mediates the parasympathetic control of the heart, controlling acceleration and deceleration of heart rate (Porges, 1996; Porges, 2007). When facing an external demand to increase metabolic output (e.g., during a novel or challenging situation), withdrawal (i.e., decrease) of parasympathetic input to the heart will result in increased heart rate, allowing individuals to shift from maintaining internal homeostasis to coping with external demands (Porges, 1996).

Thus, vagal withdrawal is considered a physiological regulation process that leads to a greater cardiac output (e.g., HR acceleration) and active coping behaviors in order to adjust to the environmental demands (Calkins et al., 2008; Porges, 1996). In addition, the vagus nerve is connected in humans to muscles in the face, head, and neck. Changes in the activity in the vagal system may manifest in changes in individuals' facial expression, neck tension, and tone of voice (Porges & Furman, 2011). Therefore, it serves an important role during the process of social engagement across multiple levels of functioning.

RSA is used to quantify vagal tone and is believed to be a marker of regulation (Beauchaine, 2001; Calkins, 2011). Individual differences in RSA reflecting regulatory processes have been indexed by both baseline RSA and changes from baseline to task (i.e., RSA withdrawal or suppression), and both of these measures have been examined in the broader socioemotional literature, including studies including behavioral inhibition explicitly. Children with lower baseline RSA have difficulty with self-regulation (Beauchaine, 2001; Porges, 1996). Higher resting baseline RSA is associated with better sustained attention (Suess, Porges, & Plude, 1994), greater behavioral reactivity (Porges, Doussard-Roosevelt, Portales, & Suess, 1994), and more sociable and exploratory behaviors (Fox, 1989).

Mixed findings also exist on the association between shyness and RSA across development. For preschoolers' who were high in shyness, lower RSA was associated with lower effortful control (Sulik, Eisenberg, Silva, Spinrad, & Kupfer, 2013). However, in other samples, shyness and RSA were not linked (Marshall & Stevenson-Hinde, 1998; Dietrich et al., 2009). In an adolescent sample, behaviorally inhibited youth exhibited lower RSA and less variability in heart rate (Balle, Tortella-Feliu, & Bornas, 2013). Generally, lower baseline RSA and less RSA suppression are considered maladaptive and are associated with more social wariness (Hastings, Kahle, & Nuselovici, 2014) and anxiety symptoms (Licht, de Geus, van Dyck, & Penninx, 2009). In general, lower baseline RSA is associated with higher risk of maladaptive social behaviors, but the findings are mixed suggesting more research is needed to pinpoint specific risk across development.

In addition to baseline RSA, the ability to suppress RSA during challenging tasks has been associated with greater self-regulation and adaptive behavioral outcomes for inhibited children across development. In our own work, RSA suppression was associated with less fear in novel situations and lower risk for social anxiety for temperamentally fearful children (Buss, Davis, et al., 2018). Moreover, fear sensitivity (i.e., higher inhibition to low-threat situations) at 24 months predicted social inhibition only for toddlers who exhibited higher averaged RSA, reflecting a failure to suppress RSA across tasks (Buss, Davis, et al., 2018). In another study from our laboratory, toddlers who suppressed RSA during a novel, putatively threatening, task engaged in more approach behaviors (Brooker & Buss, 2009), further demonstrating the link between RSA regulation and adaptive behavior.

These findings extend longitudinally as well. Infants, who showed less RSA suppression during a stranger approach task at 6 months, were more than three times as likely to be characterized in a high/stable social-fear class than in the low/steady social-fear class from 6 to 36 months (Brooker et al., 2013). Moreover, infants in the high/stable social-fear class were more likely to be rated as behaviorally inhibited at 36 months. In contrast, infants who showed greater RSA suppression were also slightly more likely to be in the decreasing social-fear class than in the slow increase class (Brooker et al., 2013). Therefore, across multiple studies the pattern of findings suggest that vagal withdrawal may buffer children who have temperamental risk from developing inhibited social behavior (Brooker et al., 2013; Cho & Buss, 2017) and from developing social inhibition and anxiety problems (Buss, Davis, et al., 2018).

Despite these previous findings supporting RSA withdrawal as an adaptive regulatory process, in other contexts, vagal augmentation or stable RSA levels from baseline to challenge may be more adaptive. For example, in a social context with playmates, preschool children who exhibited higher RSA compared to baseline had lower behavioral problems and better self-regulation (Hastings et al., 2008). In this case, RSA augmentation was considered adaptive as children recruit resources to engage in social situations. In addition, children who exhibited dysregulated fear (i.e., high-fear to low-threat contexts) showed more dynamic RSA changes in a stranger approach context compared to all other children (Brooker & Buss, 2009). Using a time-series analysis, high-fear toddlers demonstrated faster rate of increase in RSA (indexed by steeper linear slope) and a steeper decline (indexed by a quadratic slope) across the episode than non-high-fear toddlers. In contrast, non-high-fear toddlers showed a relative constant level of RSA over time (Brooker & Buss, 2009). In addition, these dynamic changes in RSA were related to less positive affect for high-fear toddlers (Brooker & Buss, 2009). The adaptiveness of RSA withdrawal always needs to be considered within a specific eliciting context (e.g., high fear vs. low fear; social vs. emotionally challenging). What is consistent, however, is that inhibited and fearful children are more likely to show maladaptive patterns of RSA during novel and social challenges.

Vagal withdrawal also plays an important moderating role in the association between parenting and children's behavioral inhibition and anxious behavior. For

example, fathers' high protective overcontrol was associated with inhibition only for preschoolers who showed less RSA suppression (Hastings et al., 2008). In contrast, fathers' supportive parenting reduced inhibition for children with less RSA suppression (Hastings, Sullivan, et al., 2008). In another study examining RSA, attachment, and behavioral inhibition, Paret and colleagues found that insecurely attached (ambivalent attachment), behaviorally inhibited preschoolers were less likely to suppress RSA to a novel situation compared to securely attached children (Paret, Bailey, Roche, Bureau, & Moran, 2015). These differences were not found for children who were low on behavioral inhibition (Paret et al., 2015). This finding is consistent with those presented earlier demonstrating an interaction between behavioral inhibition and insecure attachment in predicting increases in cortisol (Nachmias et al., 1996). In our own work, we have found similar moderating effects with RSA. We found that when mothers predicted high fear in their 24-month-old toddlers during fear-eliciting tasks, they were more likely to engage in overprotective behaviors and rate children as anxious in preschool, when toddlers were lower in baseline RSA and lower RSA suppression (Cho & Buss, 2017). Much like the previous findings with cortisol stress reactivity, these findings demonstrate the importance of the caregiving environment and the quality of parent-child relationship for how inhibited children regulate their distress and engage with their environment.

In sum, although not all studies find a consistent association between RSA (baseline or reactive) and behavioral inhibition, the pattern of findings points to a pattern of dysregulation for inhibited and anxious children across development. Specifically, lower baseline RSA and less RSA suppression to stressful and challenging situations mark a failure to engage with environment, less self and emotion regulation, greater fearful behavior, and risk for anxiety across development. Not only does this pattern of findings suggest difficulty with regulation for inhibited children on average; it suggests that those inhibited children who most consistently have difficulty regulating may be at greatest risk. Thus, RSA as a marker of regulation can be considered an important contributor to the identification of the most at-risk inhibited children.

Delta-Beta Coupling

There is increasing evidence that behavioral inhibition, and other types of extreme fearful traits (e.g., dysregulated fear), may be associated with a propensity to overregulate (Eisenberg et al., 2001; Murray & Kochanska, 2002), putting inhibited children at increased risk for developing anxiety. Although summarizing these behavioral studies is beyond the scope of this review, there is emerging literature suggesting that other processes examined at the neural level that may shed light on this question. For instance, delta-beta coupling has recently emerged as a putative biomarker of regulation (Knyazev & Slobodskaya, 2003; Phelps, Brooker, & Buss, 2016).

The coupling between slow (e.g., delta) and fast (e.g., beta) wave EEG activity is believed to reflect functional interactions between cortical and subcortical circuitry (Knyazev & Slobodskaya, 2003). Greater positive associations between delta and beta power reflect functional coherence between cortical (i.e., cerebral cortex) and subcortical (i.e., limbic) structures, and delta-beta coupling may reflect a form of top-down regulation (Knyazev & Slobodskaya, 2003). Thus, high delta-beta coupling in the context of anxiety risk is believed to reflect overcontrol or overregulation. Emerging work related to behavioral inhibition and anxiety symptoms reveals a robust link between these behavior patterns and greater delta-beta coupling in adults (Miskovic et al., 2011; Putman, 2011) and in children (Miskovic et al., 2011; Phelps et al., 2016).

We have shown that patterns of coupling in toddlers differ based on the context (i.e., high fear and low fear). In a low-fear context, high levels of fear (i.e., dysregulated fear) were associated with significant delta-beta coupling at frontal, central, and parietal electrodes, whereas low levels of fear were associated with significant coupling only at parietal sites (Phelps et al., 2016). In contrast, in a high-fear context, there were no differences in coupling between the high- and low-fear groups (Phelps et al., 2016). Consistent with other work highlighting the role of the eliciting context (Buss, 2011; Buss, Davis, et al., 2018), these findings indicate that children who exhibited dysregulated fear showed higher levels of regulation (i.e., overcontrol) at a neural level.

Event–Related Potentials (ERPs)

Specific executive processes—executive function—have also been examined in the behavioral inhibition literature, particularly as mechanisms that contribute to the development of anxiety. For purposes of this chapter, we focus primarily on the literature wherein the processes of inhibitory control and attentional control have been examined. Intrinsic traits, such as children's attention control, attention shifting, and inhibitory control, are regulated by children's executive functioning and contribute to children's lasting behavioral inhibition (Degnan & Fox, 2007). Children with behavioral inhibition who can flexibly maintain and switch their attention may be less likely to develop anxiety symptoms and more likely to demonstrate adaptive social behavior (Degnan & Fox, 2007). These executive processes can be assessed using event-related potentials (ERP). Event-related potentials measure the brain's electrophysiological response to a specific sensory or a cognitive event or a response to a stimulus. Of particular benefit, ERPs are noninvasive and can record activity at a millisecond level (Luck, 2014). Different components of the ERP wave reflect distinct brain processes.

Among the ERP components, N2 and P2 components have been repeatedly found in association with children's anxiety symptoms. The N2 component has been associated with conflict monitoring, reflecting inhibitory and attention control (Van Veen & Carter, 2002). In work closely aligned with anxiety development, these

components have been associated with affective, attentional, and cognitive processes, such as attention to and away from threat (Dennis & Chen, 2009), and have been linked to anxiety problems (Dennis & Chen, 2009; Ladouceur, Conway, & Dahl, 2010; Pérez-Edgar & Fox, 2005).

The N2 has also been correlated with executive attention and temperamental traits. For example, in 4- to 8-year-old children, increased N2 during a flanker task was associated with less efficient executive attention and lower temperamental effortful control (Buss, Dennis, Brooker, & Sippel, 2011). The P2 component has been associated with early visual perception and attention (Schupp et al., 2004) and has been found to be enhanced to negatively valenced visual stimuli (Foti & Hajcak, 2008; Huang & Luo, 2006).

Turning to the behavioral inhibition literature, there have been a number of studies examining these ERP components. In a sample of 9- to 12-year-old children, attention bias toward threat was marginally positively correlated with N2 amplitude during a concurrent dot-probe task. Furthermore, the positive association between attention bias to threat and behavioral inhibition was only evident for children who had a larger N2 (Thai, Taber-Thomas, & Pérez-Edgar, 2016). In contrast, social anxiety symptoms were negatively correlated with P2 amplitude (Thai et al., 2016). The association between attention bias toward threat and N2 amplitude has also been found in longitudinal studies. For example, behavioral inhibition assessed at age 2 was negatively associated with N2 activation in a go-no-go task at age 7, indicating greater N2 activation as behavioral inhibition increased (Lamm et al., 2014).

Therefore, larger N2 and smaller P2 seem to be risk factors for behaviorally inhibited children who are likely to develop anxiety symptoms. These ERP components have also been found to moderate the association between behavioral inhibition and anxious behavior. When N2 activation was high, toddler behavioral inhibition was positively associated with later social reticence at age 7. However, this association was not significant when N2 activation was low (Lamm et al., 2014). Likewise, the association between behavioral inhibition and social anxiety was stronger with smaller P2 compared to larger P2 amplitudes (Thai et al., 2016).

There has also been a surge of recent studies examining error-related negativity and behavioral inhibition. The error-related negativity (ERN) is an ERP component that peaks at frontocentral midline scalp recording sites and usually occurs 50–100 msec following an incorrect behavioral response (Falkenstein, Hohnsbein, Hoormann, & Blanke, 1991). A large ERN has been associated with high fear and behavioral inhibition (Brooker & Buss, 2014a) and anxiety symptoms (Meyer et al., 2013). Specifically, high-fear toddlers showed a larger ERN compared to correct-trial negativity (CRN indicates correct response negativity, used as a comparison condition to ERN) at age 4.5, compared to low-fear toddler (Brooker & Buss, 2014a). In a follow-up study, harsh maternal parenting interacted with toddler fearfulness to predict inhibition and ERN at age 4.5 (Brooker & Buss, 2014b). In other work, children who were diagnosed with an anxiety disorder at age 3 demonstrated a larger difference between the ERN and CRN at age 6 (Meyer et al., 2013). In a follow-up study with the same children, Meyer and colleagues found that punitive

parenting practices predicted ERN and ERN mediated the association between parenting and anxiety symptoms (Meyer et al., 2015).

Similar findings have also been reported in an adolescent sample. Adolescents who were high in childhood behavioral inhibition exhibited greater ERN amplitude compared to adolescents who were low in childhood behavioral inhibition (McDermott et al., 2009). In addition, in the high behavioral inhibition group, smaller ERN responses were related to lower risk for anxiety diagnosis at a trend level. For the low behavioral inhibition group, there was no relation between ERN response and anxiety diagnosis (McDermott et al., 2009). These findings suggest that greater ERN seems to be a correlate of behavioral inhibition traits and greater ERN responses maybe especially maladaptive for children who are high in behavioral inhibition.

The difference between ERN and CRN also serves as a putative risk marker for anxiety for children who demonstrated early behavioral inhibition. Specifically, toddler behavioral inhibition was associated with social phobia at age 9, but only among children who had a larger difference in amplitude between ERN and CRN at age 7 (Lahat et al., 2014). Therefore, larger difference in amplitude between ERN and CRN not only is a correlate of children's behavioral inhibition but also serves as an additional risk factor for children who already demonstrated early behavioral inhibition.

In addition to ERN, the error positivity (Pe) has also been examined in relation to behavioral inhibition. The Pe is a positive-going slow wave that follows the ERN and has a slightly more posterior scale distribution than the ERN (Falkenstein et al., 1991). Pe is believed to reflect more conscious processing of errors relative to the ERN (Falkenstein et al., 1991). In a sample of 5-year-old children, higher Pe was associated with less boldness during conversations with strangers, indicating hypervigilance in these children and a lack of efficiency in cognitive processing (Brooker, Buss, & Dennis, 2011). These findings suggest that children with highly inhibited traits tend to have enhanced performance concerns and increased vigilance (see the chapter "The Neural Mechanisms of Behavioral Inhibition" by Jarcho and Guyer and the chapter "Relations Between Behavioral Inhibition, Cognitive Control, and Anxiety: Novel Insights Provided by Parsing Subdomains of Cognitive Control" by Buzzell et al.), which may reflect a rigid and inflexible pattern of behaviors during social situations (Lahat et al., 2014).

In sum, children's behavioral manifestation of their inhibition may be reflected in the way they process salient information in reflecting higher vigilance, conflict, and error monitoring. The pattern of ERP difference is consistent with findings of children and adolescents with anxiety symptoms and disorders, suggesting that these measures may serve as additional risk markers for behaviorally inhibited children who are already susceptible to developing subsequent anxiety symptoms.

Concluding Thoughts

Despite robust evidence that behavioral inhibition is the best early predictor of anxiety, not all behaviorally inhibited develop anxiety problems. As we have discussed in this chapter, this suggests heterogeneity in behavioral inhibition and developmental trajectories of anxiety for these children. In our work, the primary focus has been on the pattern of behavior across eliciting contexts that differentiates subtypes of fearful children as evidence for the heterogeneity. This approach has enhanced the identification of which of inhibited/fearful children are at greatest risk. However, this work and the identification of behavioral inhibition, more broadly, have exclusively focused on behavioral observations despite both temperament and anxiety theory positing these traits as neurodevelopmental in nature.

Consistent with temperament theories (e.g., Rothbart & Bates, 2006), there is growing evidence that the processes of reactivity and regulation account for these extreme behavioral differences and serve as putative mechanisms by which this temperamental risk is manifest as psychopathology. As we have reviewed in this chapter, multiple physiological markers of these processes have been consistently linked to behavioral inhibition and also provide a more complete picture of anxiety risk for these behaviorally inhibited children. Rather than considering these physiological measures as correlates or moderators, researchers should move to examining physiological processes as additional indicators of behavioral inhibition, as we have suggested previously (Buss, Morales, Cho, & Philbrook, 2015). Thus, focusing on how physiological markers can enhance identification of behaviorally inhibited children thereby decreases heterogeneity in group membership and increases prediction of which fearful children are at risk for anxiety problems.

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