Inhibited Children in a Social World: Transactional and Interactive Processes

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Introduction

It is axiomatic to say that children's development is complex and multidetermined, involving both within-person and environmental influences in shaping child outcomes. However, simplistic models of child and environmental influences on children's development that treat the two as independent are clearly inadequate given the person-environment correlation and interaction apparent across the lifespan. Indeed, very early in development, the impact of environmental influences on development is moderated by children's endogenous characteristics, characteristics which themselves act to change children's environments over time. Put simply, endogenous traits do not develop in a vacuum; as noted by Rutter (1997, p. 336), "Genetic effects have to be manifest with respect to organisms developing in a particular environmental milieu, and environmental effects have to operate on organisms that differ with respect to genetically influenced individual characteristics." This complex interplay poses a challenge to developmental psychologists and psychopathologists hoping to understand how childhood vulnerabilities are related to negative outcomes, as well as how some at-risk children nevertheless show adaptive development.

An ample literature has focused on dynamic processes such as these in the context of childhood behavioral inhibition (BI and related traits such as shyness and trait fearfulness), a temperament trait capturing the tendency toward heightened

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vigilance, fearful affect, and behavioral withdrawal in response to novel social and nonsocial situations (Kagan, 2012). BI is an established risk factor for anxiety (Fox & Pine, 2012) and possibly depression; indeed, the defining features of BI overlap with symptoms of anxiety, rendering it potentially challenging to distinguish between the two based simply on observable features. Relatedly, contemporary models of trait-disorder associations acknowledge the shared etiological bases of traits and related disorders (Pérez-Edgar & Guyer, 2014), such that distinctions between "state" manifestations of disorder and associated "traits" are potentially limited in value, at least when considering causal factors. Put differently, a key implication of these models is that those with elevated trait vulnerability (e.g., BI) possess at least some of the causal factors for disorder (e.g., anxiety), factors which interact with other sources of risk to influence outcomes.

Consistent with these ideas, high BI in childhood shows complex relations with child outcomes, and most children high in BI do not develop internalizing problems (Liu & Pérez-Edgar, 2019; Pérez-Edgar & Guyer, 2014). Indeed, in some contexts, higher BI may be beneficial; for example, inhibited or introverted individuals tend to be more deliberate and harm-avoidant (Carver, 2005; Smits & Boeck, 2006), which may prove useful in many contexts. Like all vulnerabilities, BI has a probabilistic rather than deterministic influence on development, with context playing a key role in determining whether BI is maladaptive. Thus, although child BI is expressed within multiple sociocultural and interpersonal environments, suggesting that those who find navigating interpersonal interactions challenging are at risk, many inhibited children do not develop psychopathology, and there is tremendous variability in their developmental trajectories (Henderson, Pine, & Fox, 2015).

In this chapter, we will review the literature exploring the processes by which BI and related constructs influence children's development. Historically, observational indices of behavior have been treated as the gold standard by which BI is indexed (Kagan, 2002), with parent- and self-reported BI used as other indices of trait BI. However, we will draw upon multiple vantage points for understanding processes relevant to BI, including indices of attention and other cognitive processes, psychophysiological approaches, structural and functional neuroimaging techniques, and genetic influences, when these are thought either as reflective of concomitant processes in BI or as potentially etiologically significant. We also review contextual influences likely relevant to the ontogeny of BI. Unsurprisingly, much of the extant literature has focused on caregiving and the broader sociocultural environment of the child, but we will also consider what we refer to as *the context of the individual*, by which we mean other child factors that may interact with BI, such as biological sex, gender, and other child traits. Broadly, our goal in this chapter is to highlight the processes relevant to understanding the pathways by which BI shapes outcomes.

Caregiving, the Early Home Environment, and the Inhibited Child

Parents and other caregivers are by far the most prominent influence on the early environment in which children develop. It is, therefore, unsurprising that parenting behaviors have received a great deal of attention as potential influences that operate in conjunction with child BI to predict development. As noted by Buss and Kiel (2013), parenting can play a formative role in driving the extent to which children approach/engage with novelty. Investigators have been interested in the interplay between child BI and caregiving that promotes (or fails to promote) engagement with novelty, positing a curvilinear pattern such that parents who discourage children from interacting with unfamiliar situations and those who use coercive or insensitive efforts to promote interaction with the unfamiliar are both associated with negative child outcomes.

In line with this model, we focus on two types of parenting behaviors commonly studied in the BI literature (Buss & Kiel, 2013; Kiff, Lengua, & Zalewski, 2011), overprotection and intrusiveness. Overprotective parenting is conceptualized as parenting behaviors that restrict children's exploration in novel environments, as well as the provision of excessive comfort when child distress arises in novel contexts, thereby potentially reinforcing avoidance (Ungar, 2009). Intrusive parenting is defined as inappropriately rigid parental control of children's behaviors (Wood, 2006); for children with BI, intrusive parents typically push them to interact with unfamiliar situations in an insensitive, forceful manner. While different labels have been used to refer to the same or highly similar parenting constructs (e.g., oversolicitous parenting, oversensitivity, overcontrol, low autonomy granting, parental derision), we use the terms *overprotection* and *intrusiveness* throughout. We will review available literature on both trait-parenting interactions as well as mediating processes implicated in BI and care. Of note, although both moderation and mediation are likely possible, the majority of the BI-parenting literature has focused on one or the other.

With respect to how protective and intrusive parenting behaviors moderate the effect of BI on child outcomes, compared to equally inhibited children with overprotective parents, inhibited toddlers and preschoolers of less protective parents tend to show lower stability of BI and a decreased likelihood in developing anxious behaviors (Hastings et al., 2008; Rubin, Burgess, & Hastings, 2002). For behaviorally inhibited toddlers, lower maternal sensitivity or protection was associated with fewer child anxious behaviors both concurrently (Mount, Crockenberg, Jó, & Wagar, 2010) and prospectively (Park, Belsky, Putnam, & Crnic, 1997). Although the mechanisms underlying this interactive effect are unclear, overprotective parenting may prevent inhibited children from developing coping skills when faced with novelty; as a result, these children's inhibited and anxious responses to novelty are sustained and exacerbated over time.

Intrusive parenting shows similar patterns in moderating the effects of early child BI on socioemotional outcomes. For instance, toddlers' inhibited behaviors at age 2

predicted their social reticence at age 4, but only when mothers showed more intrusive behaviors at age 2 (Rubin et al., 2002). Inhibited toddlers of more derisive and critical mothers showed sustained inhibition and social reticence, compared to their peers with non-derisive mothers (Johnson et al., 2016; Rubin et al., 2002). For inhibited children, intrusive parenting may result in heightened negative emotional arousal in them when they are already challenged by the novel environment, which may enhance their feelings of being out of control (Chorpita & Barlow, 1998), overwhelm their coping capacities, and further disrupt their ability to self-regulate (Nachmias, Gunnar, Mangelsdorf, Parritz, & Buss, 1996). Overall, the two seemingly very different parenting constructs, overprotection and intrusiveness, show similar effects in moderating the relations between BI and outcomes, perhaps due to the fact that both constructs prevent children from effectively learning strategies to cope with novelties. This line of studies suggests that the effects of early BI may be potentiated by variations in parenting behaviors, which constitute a primary component of the child's immediate socioemotional environment.

In addition to the interactions between BI and parenting in predicting socioemotional outcomes, recent studies emphasize the bidirectional relations between BI and parenting. For example, overprotective parenting at age 2 predicted children's fearful inhibition at age 4, with the stability of children's inhibited behaviors controlled for (Rubin et al., 2002). For preschoolers, protective parenting predicted child inhibited and fearful behaviors a year later, above and beyond the stability of child inhibition (Edwards, Rapee, & Kennedy, 2010). Over and above the stability of negative reactivity during infancy, certain "less protective" parenting patterns observed at 27 and 33 months, such as lower sensitivity, less positive affect, and greater intrusiveness, were prospectively associated with lower child inhibition at 36–37 months old (Park et al., 1997). Another study of toddlers, however, failed to observe relations between overprotective parenting at age 2 and parent-reported BI at age 4 (Rubin, Nelson, Hastings, & Asendorpf, 1999). Overall, the work focusing on mediation and moderation indicates that parental overprotection may serve to strengthen associations between BI and negative outcomes.

Relatively less work has been conducted in older children. In a longitudinal cohort of school-age children, higher parental rejection at age 9 predicted modest increases in fearful inhibition and in turn internalizing problems, at age 11, with the stability of inhibition accounted for Lengua (2006). Likewise, less consistent parental discipline at age 9 predicted greater child inhibition at age 10; however, inconsistent discipline at age 9 predicted lower child inhibition at age 11 (Lengua, 2006; Lengua & Kovacs, 2005). These inconsistent predictive patterns at age 10 and 11 may reflect changes that unfold as youth are transitioning into adolescence, such that they might perceive highly consistent parenting as overcontrolling and inconsistent parenting as more autonomy granting, resulting in decreased inhibition.

Child BI also seems to elicit certain parenting behaviors, with work focusing on the impact of child BI on protective parenting. In particular, compared with their non-inhibited peers, inhibited children are more likely to elicit protective behaviors from their caregivers, especially in contexts where BI is relevant (i.e., novelty). Longitudinal studies find that parent-reported inhibition in toddlers predicted

parents' overprotective behaviors and disencouragement of independence in the future, over and above the stability of parenting (Hastings & Rubin, 1999; Rubin et al., 1999). Overprotection may in turn maintain and reinforce toddlers' fearful inhibition and increase their risk for later anxiety, playing a mediating role in linking early BI and later anxiety (Kiel & Buss, 2009). A similar pattern of BI-to-parenting was observed in older children: with the stability of parenting controlled for, higher fearful inhibition at age 9 predicted increased parental acceptance a year later and decreased parental rejection over the next 2 years (Lengua & Kovacs, 2005).

Most of the existing literature has used parent self-reported (or child-reported when applicable) questionnaires to measure parenting behaviors. While questionnaires are an economical and efficient means of collecting data, they are subject to various reporting biases (e.g., social desirability) and contribute to spurious or inflated correlations between constructs due to shared method and mono-informant variance when the developmental outcome is also measured by questionnaires from the same respondent. Thus, independent measures of key constructs provide a more stringent test of relations between child and family factors and youth outcomes. In recent work, we used observational measures of parenting to provide novel information for BI-to-parenting associations. Structured parenting is characterized by caregiving strategies that provide consistent guidance and scaffolding for the child and regulate child behaviors and emotions by providing specific instructions and limit setting, especially when the child is facing challenging situations (e.g., Barber, 1996; Pomerantz & Eaton, 2001). Along the continuum of "encouragement to approach/engage with novelty" (Buss & Kiel, 2013), structured parenting can be mapped to the middle area of the spectrum, featured by a balance between warmth and limit setting. In our study, child BI observed at age 3 predicted more structured parenting observed at age 5, which in turn predicted fewer child internalizing and attention-academic problems at age 8 (Liu, Kryski, Smith, Joanisse, & Hayden, 2019).

These findings are somewhat inconsistent with past work showing that children high in BI elicit overprotective parenting (Hastings & Rubin, 1999; Rubin et al., 1999). This may reflect the fact that our data were drawn from low-risk, community-dwelling families who may be better equipped to manage difficult child behaviors with appropriate caregiving. However, this divergence might also reflect the fact that different measurements of parenting assess different aspects of this construct. Specifically, questionnaires tend to emphasize the parent's general attitudes toward child-rearing (e.g., "I encourage my child to be independent of me"; Block, 1981), whereas observational tasks capture more concrete parenting behaviors within a specific situation (e.g., when the parent and child are working together to complete a task). This highlights the importance of using multiple measurements to tap into multiple levels and facets of a particular construct, which may play different roles in influencing developmental pathways.

Overall, the findings reviewed above indicate that parents' caregiving behaviors play an important role in shaping BI-anxiety links. For at least some children high in BI, gentle parental encouragement to approach and engage with novel situations, alongside the provision of specific instructions and effective coping skills, may place children on a more adaptive developmental pathway toward optimal outcomes.

Accordingly, prevention and intervention efforts that promote parenting strategies of this kind may be helpful.

BI and Cognition: Attentional Bias to Threat

BI likely interacts with individual's cognitive system as well, especially the attentional processes. To the extent BI and attention are somewhat independent of one another, attentional processes may serve as a "context" that interacts with BI to predict child outcomes. Cognitive theories of psychopathology propose that altered or "biased" patterns of cognition may serve as an important causal mechanism in the development of mental health problems (Clark & Beck, 1999); for anxiety in particular, early attentional bias (AB) toward negative information is thought to play a causal role in potentiating anxiety problems (Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & van Ijzendoorn, 2007). This notion has been supported by empirical evidence generated by both longitudinal studies (MacLeod & Hagan, 1992) and experimental manipulation designs (MacLeod, Rutherford, Campbell, Ebsworthy, & Holker, 2002). Based on this literature, BI researchers have become interested in exploring the AB profiles of children with BI and the relations between the two anxiety vulnerabilities, BI and AB, in shaping children's developmental pathways toward anxiety.

The psychopathology literature documents that relative to healthy controls, anxious individuals are typically characterized by heightened AB toward negative, especially threatening, information (Bar-Haim et al., 2007). Along this line, BI studies have examined the profiles of AB toward threat in behaviorally inhibited children, but with mixed findings reported. In the first study of AB in children with BI, adolescents with early childhood BI, but without any clinical diagnosis of anxiety disorder, showed elevated AB toward threat compared to their peers without early history of BI (Pérez-Edgar et al., 2010). However, this is the only study that found heightened threat AB in behaviorally inhibited youth, while studies in other behaviorally inhibited samples failed to observe elevated AB on the behavioral level in youth with BI. This might be due to the fact that attention paradigm commonly used to measure AB, the dot-probe task, has suboptimal psychometric properties (Rodebaugh et al., 2016) and is not able to capture the nuanced individual differences among nonclinical, behaviorally inhibited children.

A more recent, small neuroimaging literature has emerged by combining the dot-probe paradigm with neuroimaging techniques to yield indices of the neural substrates of AB in youth characterized on BI. The fMRI measures of AB are proven to be more reliable than the behavioral measures of the dot-probe paradigm and provide new evidence for the differences in AB between BI and non-BI individuals. A recent study found that 9- to 12-year-old children with high BI displayed greater activation in dorsolateral prefrontal cortex (dlPFC) than their non-inhibited peers, when they had to shift attention away from threat (Fu, Taber-Thomas, & Pérez-Edgar, 2017). The dlPFC area supports the maintenance of executive control, such

as voluntary attention allocation to support task-required performance in the presence of threat-related distractors (Bishop, 2008, 2009; Luks et al., 2007). Young adults with a history of stable early childhood BI showed more negative fronto-amygdala connectivity in response to angry faces, compared with individuals without early BI (Hardee et al., 2013). In both studies, the magnitude of neural activation was associated with anxiety symptoms. Further, these neural activation patterns appear to parallel those observed in clinically anxious adolescents. For instance, when shifting attention away from threat, anxious adolescents show greater dlPFC activation (Telzer et al., 2008) and attenuated amygdala deactivation (Price et al., 2014) than healthy controls. That youth elevated in BI show similar neural activation to those with anxiety suggests that these shared neural patterns during attentional processing may serve as one of the potential mechanisms underlying the pathways from BI to later anxiety.

More consistent findings come from work testing the interaction between BI and AB in predicting youth's anxious symptoms and behaviors. In other words, instead of conducting between-group comparisons, these studies focus on whether the BI-anxiety association is moderated, or strengthened, by high threat AB. In a longitudinal study, early-childhood BI prospectively predicted increased social withdrawal behaviors in adolescence, but only for adolescents who also showed higher threat AB (Pérez-Edgar, Bar-Haim, et al., 2010). Toddlerhood BI was prospectively associated with greater social withdrawal at age 5, only for children with greater threat AB concurrently at age 5 (Pérez-Edgar et al., 2011). In a different longitudinal cohort, middle childhood BI prospectively predicted social discomfort during adolescence, only for youth with altered patterns of attentional processes during infancy, including low sustained attention to targets and heightened attentional vigilance toward distractors (Pérez-Edgar et al., 2010). These observed moderation patterns suggest that for youth with early BI, the presence of heightened AB may strengthen the link between BI and later anxiety, whereas the absence of threat AB may prevent them from getting onto a maladaptive developmental pathway toward anxiety outcomes. This suggests that training inhibited individuals to shift their attention away from threat might be an effective way to diminish their anxiety symptoms and reduce risk for developing clinical anxiety (Liu, Taber-Thomas, Fu, & Pérez-Edgar, 2018).

BI and Cortisol

Recent work has focused on understanding the physiological underpinnings of BI to identify biobehavioral substrates that may underlie links between BI and later psychopathology (Buss & Kiel, 2013; Fox, Henderson, Marshall, Nichols, & Ghera, 2005). The majority of this work has focused on cortisol, the end product of the hypothalamic-pituitary-adrenocortical (HPA) system response to stress. Broadly, BI-related constructs (e.g., fear, shyness, social withdrawal) have been linked with disrupted cortisol functioning, including heightened reactivity and baseline

production (see Buss & Kiel, 2013, for review of biological correlates and mechanisms of BI).

The link between BI and stress physiology, however, may be moderated by environmental factors such as parenting. For example, higher cortisol reactivity may uniquely be associated with fearful behavior in the context of disrupted parenting and/or family processes, such as insecure attachment or maternal stress (Essex, Klein, Slattery, Goldsmith, & Kalin, 2009; Nachmias et al., 1996). Similarly, children with heightened cortisol reactivity and parental social anxiety are at the highest risk for social anxiety (Poole, Van Lieshout, McHolm, Cunningham, & Schmidt, 2018). Importantly, this suggests that the association between BI and altered stress physiology is complex and influenced by complex environmental inputs (Buss & Kiel, 2013; Gunnar & Adam, 2012).

Neural Correlates of BI

Much of the early work on the neural correlates of BI was based on animal models finding that the amygdala, which becomes functional shortly after birth, is directly linked to negative reactivity (e.g., distress cries, limb movements) in response to novelty during infancy (Kagan, 2012). The amygdala is a hub-like brain structure within a distributed network that underlies a multitude of emotion-related processes across development (Scherf, Smyth, & Delgado, 2013). The direct examination of amygdala in the context of BI, however, was not possible until neuroimaging techniques, such as fMRI, became accessible (Schwartz & Rauch, 2004). Earlier work on the neural correlates of BI relied on more accessible neural measures such as EEG and ERP and startle EMG (Schmidt & Fox, 1998), which are hypothesized to be directly associated with the hypersensitive amygdalar function (White, Lamm, Helfinstein, & Fox, 2012). Investigation of the neural foundations of BI has found shared neural correlates between BI and anxiety problems, supported by evidence generated by different neural measures including EEG, ERP, and fMRI. For example, children with high BI show heightened vigilance to the behavioral errors they made indicated by the modulation of the ERP component, error-related negativity (McDermott et al., 2008); this parallels ERP findings in anxious individuals (Meyer, 2017). The shared neural correlates between BI and anxiety might serve as a potential mechanism that tethers the two along the developmental pathway. Due to space limits, the present chapter focused on research related to frontal EEG asymmetry and fMRI correlates in behaviorally inhibited children.

Frontal EEG asymmetry is typically calculated as a difference score of alpha band activity between left and right frontal regions. Right frontal EEG asymmetry (i.e., greater alpha activity in the right than left frontal region) is associated with withdrawal tendencies, while left frontal EEG asymmetry is related with approach motivations (Davidson, 2004). In the psychopathology literature, greater right frontal EEG activity has been observed in clinically and subclinically anxious and depressed individuals (Field, Diego, & Hernandez-Reif, 2009; Thibodeau,

Jorgensen, & Kim, 2006). Similar patterns have also been reported in the BI literature. Negatively reactive infants and behaviorally inhibited children show greater right frontal EEG activity at rest (Finman, Davidson, Colton, Straus, & Kagan, 1989; Hane, Fox, Henderson, & Marshall, 2008) or when performing tasks designed to evoke fearful and withdrawal responses (Theall-Honey & Schmidt, 2006). Right frontal EEG asymmetry at 9 months prospectively predicted the stability of inhibition from infancy to age 4 (Fox, Henderson, Rubin, Calkins, & Schmidt, 2001); in another sample of inhibited children, stability in right frontal asymmetry from age 3 to 10 accounted for stability of their inhibited behaviors (Davidson & Rickman, 1999).

The right frontal EEG asymmetry found in inhibited children may reflect ipsilateral projections from the right amygdala, which is presumed to receive greater visceral inputs than the left amygdala (Kagan, 2002). When inhibited children show heightened bodily responses when facing novel stimulations, their right amygdala became more activated, which then leads to higher alpha activity in the right frontal regions. EEG source modeling research shows that frontal EEG asymmetry is localized in, and thus directly reflects, dorsolateral prefrontal cortex (dlPFC) activity (Shackman, McMenamin, Maxwell, Greischar, & Davidson, 2009). Neuroimaging evidence supports the functional lateralization of dlPFC that the left dlPFC is involved in approach, goal-related, motivational processes and right dlPFC in withdrawal-related tendencies (Spielberg, Stewart, Levin, Miller, & Heller, 2008). Activation of right dlPFC during withdrawal-related processes might further support threat-related vigilance (Davidson, 2004). These patterns yielded by different measures converge to support the functional lateralization of dlPFC in relation to approach-inhibition behavioral tendencies, including child BI.

As neuroimaging technology has become increasingly accessible, recent work has more directly examined the hypothesized amygdala-based neural substrates of BI, documenting heightened amygdalar activation in inhibited individuals in response to novel or emotional stimuli, especially when stimuli are negative in valence. Again, these patterns parallel what has been observed in clinical anxiety (e.g., Monk et al., 2008). For instance, young adults identified as behaviorally inhibited during toddlerhood showed exaggerated bilateral amygdalar activation in response to novel faces, compared with their peers without a history of early BI (Schwartz, Wright, Shin, Kagan, & Rauch, 2003). Similar evidence for atypical amygdalar activation in young adults characterized with early BI includes faster latency in response to novel faces (Blackford, Avery, Shelton, & Zald, 2009) and difficulty in habituating to repeatedly presented faces (Blackford, Allen, Cowan, & Avery, 2013). When 12-year-old adolescents had to subjectively rate their feelings of fear in response to emotional faces, those with a history of early childhood BI showed greater amygdalar activation than their peers without BI (Pérez-Edgar et al., 2007). Collectively, these findings support the initial proposal of the amygdala as the primary neurobiological basis of BI and highlight its role as a shared neural foundation between BI and anxiety (e.g., McClure et al., 2007; Monk et al., 2008; Stein, Goldin, Sareen, Zorrilla, & Brown, 2002; Thomas et al., 2001). For individuals with a history of early childhood BI, the atypical amygdalar function may help

sustain their early temperamental risks over time and contribute to the later emergence of maladaptation.

Another line of recent neuroimaging studies suggest that BI may also be associated with neural functions that are implicated in reward processing, such as striatal function (Caouette & Guyer, 2014). Overall, this literature suggests that behaviorally inhibited youth of different ages show reward-related striatal hypersensitivity. For example, in a stratified incentive task, while adolescents with or without early BI showed similar behavioral performance, inhibited adolescents showed heightened striatal activation in response to incentives compared with their non-inhibited counterparts (Guyer et al., 2006). When the reward outcome was irrelevant to participants' task performance, adolescents with or without early BI showed comparable striatal activation; when the reward was contingent upon performance, adolescents with early BI showed heightened striatal activation than the non-inhibited group (Bar-Haim et al., 2009).

Adolescents with early BI also showed greater striatal activation in response to immediate negative feedback for their behavioral performance than their non-inhibited peers (Helfinstein et al., 2011). Further, heightened striatal activation was found in 10-year-old children with early BI in comparison with their non-inhibited peers; for inhibited children, the magnitude of striatal activation was further related with their social anxiety symptoms, both concurrently and prospectively (Lahat, Benson, Pine, Fox, & Ernst, 2018). The reward-related hypersensitivity may reflect the participants' worry regarding uncertain outcomes, concern over their performance being evaluated, or excessive motivation to avoid losses (Guyer, Masten, & Pine, 2013). Again, parallel patterns of heightened striatal response to incentives have been reported in adolescents with clinical social anxiety, which is associated with dysfunctions in the striatal dopaminergic system (Guyer et al., 2012). In addition to hyperreactive amygdala, atypical striatal function may constitute another shared neural correlate between BI and anxiety, serving as an additional neurocognitive vulnerability to anxiety for children with BI.

In addition to serving as neural correlates of BI, specific patterns of activity within these areas may also moderate developmental pathways between BI and later outcomes. Similar to the moderating role of threat bias discussed earlier in this chapter, extreme patterns of neural dysfunction may sustain the stability of BI and strengthen its link with later anxiety. These moderation patterns suggest that the coupling of more than one vulnerability may create a "richer" context of risk, which potentially increases the probability of developing maladaptive pathways. A recent study of 9–12-year-old children characterized by early BI found that the association between BI and anxiety symptoms was strongest for those who also showed higher AB toward threat (cognitive marker of risk) and right frontal EEG asymmetry (neural marker of risk). On the other hand, inhibited children with greater left frontal alpha activity and attentional avoidance of threat showed lower anxiety symptoms (Vallorani et al., Unpublished manuscript). These findings again emphasize that BI, as a temperamental risk alone, does not necessarily lead to negative developmental outcomes; rather, specific developmental pathways and outcomes are shaped by the

interrelations between factors from different systems within the individual, as well as between the individual and the environment (e.g., parenting).

Genetic Underpinnings of BI

Consistent with the developmental psychopathology tradition, genetic underpinnings of BI have been investigated in efforts to identify genetic markers of BI and genetic contributors to multifinality. This work has implicated genetic markers related to the serotonin (e.g., 5-HTT serotonin transporter) and dopamine (dopamine receptor D4 gene, brain-derived neurotrophic factor gene) systems. We acknowledge that concerns have been raised regarding the replicability of this literature (Hewitt, 2012); however, we provide an overview here with the goal of informing efforts at replicability and future hypothesis testing of genetic mechanisms using methods more robust than those currently widely available. Nevertheless, we encourage the reader to evaluate the findings we present critically and in light of the broader literature.

Serotonin Transporter

The majority of extant research on the serotonin system has focused on a functional polymorphism in the promoter region of the serotonin transporter (5-HTT), which consists of a short and long allele. The short allele is associated with reduced serotonin uptake and 5-HTT transcription (Hariri et al., 2002; Lesch et al., 1996) and has been associated broadly with negative emotionality in adults (Munafo et al., 2003; Munafò, Durrant, Lewis, & Flint, 2009). Regarding BI specifically, the short alleles of the 5-HTT promoter region polymorphism confer increased vulnerability for behavioral inhibition (Whisman, Richardson, & Smolen, 2011). In particular, Whisman et al. (2011) found among undergraduates that having one or two copies of the low-expressing alleles was uniquely associated with stronger endorsement of the behavioral inhibition system on the BIS/BAS self-reported scales (Carver & White, 1994), a construct with considerable conceptual overlap with BI.

Findings regarding the 5-HTT promoter region and BI in children are equivocal. For example, some studies have not found associations between the 5-HTT gene and BI (Schmidt, Fox, Rubin, Hu, & Hamer, 2002). Considering related constructs such as shyness, some work has found that the long form of the 5-HTT gene is associated with questionnaire measures of shyness (Arbelle et al., 2003), whereas others have found that short-short 5-HTT allele status is associated with heightened shyness indexed via questionnaire and behavioral observation (Battaglia et al., 2005). Hayden et al. (2007) demonstrated that preschool-aged children with one or more long alleles of the 5-HTT gene were more nervous during observational laboratory tasks, whereas children homozygous for the short alleles were rated as significantly

shyer via maternal report. More recently, these equivocal findings have been extended by results implicating the 5-HTT in gene-environment interactions.

Multiple studies now support that the link between the 5-HTT gene and BI may be moderated by social factors. Fox et al. (2005) demonstrated that children with the short 5-HTT allele only had increased risk for BI in middle childhood in the context of low social support. Similarly, others have found that children with the short allele demonstrated less continuity in BI over time, suggesting that the short variant increases plasticity to contextual influences (Johnson et al., 2016). This is consistent with a growing literature documenting the 5-HTTLPR gene in differential susceptibility to environmental input, such that children with the short allele may be particularly sensitive to positive and negative environmental factors.

Brain-Derived Neurotrophic Factor (BDNF)

Brain-derived neurotrophic factor (BDNF) is a protein that underlies neural plasticity (Schinder & Poo, 2000). The BDNF val66met polymorphism involves a substitution at codon 66 that is associated with reduced secretion of the BDNF protein that has been associated with risk for anxiety disorders (e.g., Suliman, Hemmings, & Seedat, 2013), perhaps due to associated changes in neural architecture (e.g., Gatt et al., 2009). Regarding BI in particular, the BDNF met allele is uniquely associated with endorsement of behavioral inhibition scales (Johnson, Carver, Joormann, & Cuccaro, 2016). The BDNF met allele may also influence the consistency of BI across development, as Vandermeer et al. (2018) found that children with the met allele had less stability in BI from ages 3 to 6. It is essential for future research to specify how multiple genes interact with environmental input in order to identify how BI changes and confers risk for psychopathology across development (e.g., Green et al., 2017).

Conclusion and Future Directions

We revisit our initial and widely accepted assertion that children's development is highly complex, involving person-environment interactions and correlations. The simplicity of this statement, as well as its widespread acceptance in the field, belies the challenge of effectively unpacking influences on children's development, specifically behavioral inhibition and social factors in the current context. Here, we highlight a few future directions we think will be of benefit to the field in terms of meeting this challenge.

Moving forward, the complex role of BI in development necessitates longitudinal approaches toward understanding the natural progression of the trait, as well as how it may both elicit and interact with context in nonrandom ways. It is not as though longitudinal studies of BI are lacking; however, as we have noted elsewhere

with respect to child development more broadly (Hayden & Harkness, 2020), research aimed at understanding the development of BI necessitates developmentally sensitive yet equivalent indices of the construct for use during childhood and adolescence. Thus, we encourage psychological scientists to revisit popular measures of BI toward the goal of establishing their equivalence when applied to different developmental stages. While we understand that work such as this is much easier to do with questionnaire assessments, given the potential limitations of these, we also encourage investment in developing and validating observational measures of BI that function equivalently across childhood. Put simply, the construct validity of our assessment tools places constraints on the strength of any conclusions we might draw with respect to development, whether BI or other child factors are the construct of interest.

We also acknowledge that no single methodological approach (e.g., naturalistic longitudinal methods) will suffice with respect to answering questions about the interplay between BI and contextual influences. Given the nonrandom associations between BI and contextual variables, experimental designs that contrast children who vary in BI in terms of reactivity to experimentally manipulated stimuli will continue to prove useful in understanding the interactions between causal forces that shape BI and its relation to adaptive and maladaptive outcomes (e.g., Pérez-Edgar et al., 2011). Controlled studies that aim to better unpack the mechanisms and processes by which BI renders some children vulnerable to anxiety will also prove useful in this regard. For example, there is evidence from experimentally controlled studies to support the effectiveness of attentional bias modification (ABM) in youth at risk for anxiety based on elevated BI (Liu et al., 2018). However, despite the potential efficacy of the approach in terms of ameliorating symptoms, it is unclear whether attention, the purported mechanism of risk, actually changes as a result of ABM (Price et al., 2016). This may stem from the use of psychometrically problematic yet widely used indices of attentional bias (e.g., the dot-probe paradigm; Rodebaugh et al., 2016). Hence, even controlled experimental studies will benefit from close scrutiny of measures, including those which have become standard in the field given that the extent to which an assessment tool is widely used does not necessarily indicate adequate psychometric properties or construct validity (e.g., Kotelnikova, Olino, Klein, Kryski, & Hayden, 2016). Controlled studies manipulating change in putative causal mechanisms (biological or otherwise), when equipped with rigorous assessment tools, will continue to prove useful for informing developmental theory with respect to BI, as well as potentially informing preventative measures.

Understanding the pathways by which BI might foster positive outcomes merits further research attention. Certainly, avoidance of harm and attention to threat are useful in dangerous environments, fostering health and even survival, but BI may also foster superior outcomes even in more typical contexts for child development (e.g., school competence and peer liking; Chen, Chen, Li, & Wang, 2009). Ties between child BI (and related constructs; Aron, Aron, & Jagiellowicz, 2012) and outcomes may follow a pattern referred to as *differential susceptibility* (in which an individual difference factor serves to increase sensitivity to an array of positive and

negative environmental factors, such that individuals with this "susceptibility" are not only more vulnerable to stress but are also more likely to thrive in enriched environments; Boyce & Ellis, 2005). However, as we have noted elsewhere (Hayden & Durbin, 2018), testing such models requires the psychological scientist to be mindful of the distinction between the absence of negative outcomes and the presence of superior functioning. This is critical in light of the small effect sizes and probabilistic nature of most putative markers of susceptibility, including BI, whereby most with the hypothesized vulnerability do not develop disorder, yet also may not show especially positive outcomes. Similarly, contextual factors thought conducive to especially superior developmental outcomes cannot merely index the absence of "risky" environments (e.g., the absence of negative caregiving) if the goal is to adequately test differential susceptibility.

Many scientists interested in BI are likely to self-identify as developmental psychopathologists; thus, it is perhaps unsurprising that the field has embraced a multilevel approach to understanding and assessing BI. Such an approach will continue to enhance the field and also has implications for training. Collaboration across fields and transdisciplinary approaches to graduate training are essential toward understanding the complex and multidetermined processes that account for the diverse developmental trajectories of children with BI. We note that it is not unusual for psychological scientists interested in BI to specialize in behavioral, psychophysiological, and neuroscientific methods. This tendency to choose methodologies and collaborations based on available data, rather than on familiarity, is laudatory. However, we also encourage scholars to avoid choosing research tools based on which methods are perceived to be the most important or sophisticated (Hayden & Harkness, 2020; McFall, Treat, & Simons, 2015). For example, the long tradition of laboratory-based behavioral assessments has yielded important insights into the nature of BI, even though there might be a tendency to view such approaches as primitive compared to the tools available for neuroimaging. Given the paucity of evidence to support reliance on one "level of analysis" over another, it is important to validate newer approaches against those which have already been fit within nomological networks (Cronbach & Meehl, 1955).

In closing, those who study BI are fortunate to do so during a time when cutting-edge tools are available and increasingly affordable and collaboration and replication are increasingly seen as essential toward fostering true progress in psychological science. These factors, considered as a whole, leave us well poised to shed new light on how, when, and for whom vulnerability related to BI leads to maladaptation. We eagerly await the continued growth of this rich area of developmental science.

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