ANNUAL REVIEWS

Annual Review of Developmental Psychology

Two-Hit Model of Behavioral Inhibition and Anxiety

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Annu. Rev. Dev. Psychol. 2023. 5:239–61

First published as a Review in Advance on July 5, 2023

The *Annual Review of Developmental Psychology* is online at devpsych.annualreviews.org

https://doi.org/10.1146/annurev-devpsych-120621-043722

Keywords

behavioral inhibition, anxiety, two-hit model, infancy, adolescence, developmental origins

Abstract

Four decades of research have examined the antecedents and consequences of behavioral inhibition (BI), a temperament profile associated with heightened reactivity to sensory stimuli in infancy, reticence toward social cues in childhood, and the later emergence of social anxiety in adolescence. This review proposes that a two-hit model can supplement prior work to better understand these developmental pathways. Specifically, time limited experiences ("hits") centered in infancy and adolescence stress idiosyncratic BI-linked processes that uniquely trigger the developmental pathway from temperament to disorder. To illustrate, we focus on caregiver distress in infancy (including fetal development), social reorientation in adolescence, and their impact on malleable attentional and cognitive systems. These are developmental challenges and processes that go to the heart of the BI phenotype. Finally, we note open questions in this conceptual model, potential caveats, and needed future research.

Contents

INTRODUCTION

Anxiety disorders—worries and fears that are enduring, excessive, decontextualized, and developmentally inappropriate—afflict nearly 1 in 10 children in the United States (Bitsko et al. 2022). These anxious feelings can interfere with a child's functioning across social contexts, which may perpetuate the child's concerns and increase their risk for other mental health concerns, including depression and substance misuse (Bitsko et al. 2018, Pine et al. 1998, Regier et al. 1998). Clarifying why specific children are markedly more susceptible to anxiety may alleviate foreseeable distress among these individuals through targeted prevention efforts (Chronis-Tuscano et al. 2022).

Childhood temperament, particularly behavioral inhibition (BI), is a strong predictor of future anxiety problems (Sandstrom et al. 2020). BI is a temperament characterized by reticence in situations that are novel, particularly if social in nature. BI can be readily captured beginning in the second year of life (Fox et al. 2001, Kagan et al. 1984) and is preceded by marked motoric and affective reactivity to sensory stimuli as early as 4 months of age (Fox et al. 2015). Approximately 40% of behaviorally inhibited children go on to develop an anxiety disorder in adolescence, most commonly social anxiety (Clauss & Blackford 2012). As a result, BI is the strongest trait-level indicator of anxiety risk detectable in early life. Despite its active role in the etiology of anxiety, BI is often treated as a static marker that emerges early and then remains immutable, simply signaling risk—much like the check engine light in a car. Yet, we know that BI, in and of itself, is a dynamic construct that is shaped by multiple internal and experiential forces (Pérez-Edgar & Fox 2018).

In this article, we argue that a two-hit model (Knudson 1971) may help characterize the link between BI and anxiety. The "hits" we focus on in this review coincide with sensitive periods of development, windows of plasticity that uniquely encode experience to facilitate new and adaptive learning (Gabard-Durnam & McLaughlin 2020). Sensitive periods are built around experience-expectant mechanisms that are primed to receive specific information to establish foundational brain circuits. We argue that experiential hits, when they occur within putative sensitive periods, will capitalize on epochs of enhanced plasticity to shape specific socioemotional profiles and probabilistically modulate subsequent developmental trajectories (Guyer et al. 2018).

This process is most potent when the hits coincide with distinct developmental challenges faced by an individual. We contend that a first hit is carried by experiences that adaptively tune malleable attentional and affective systems (Pérez-Edgar 2018). In this case, the proposed initial hit conveys environmental uncertainty, possibly threat, and may come in the form of caregiver distress (i.e., perceived stress, anxiety). This functional tuning, occurring either in gestation or infancy, precedes the onset of the observed BI phenotype. The calibration of implicated mechanisms, canalized following sensitive period closure, may then contribute to the interpersonal difficulties characteristic of BI in childhood, such as forming and maintaining peer relationships (Rubin et al. 2009). This early hit may leave the child vulnerable to a second hit in later development. We posit that, for children with BI, the probability of developing an anxiety disorder increases if the second hit occurs in adolescence, a sensitive period for the calibration of cognitive and affective systems (Fuhrmann et al. 2015, Sisk & Gee 2022). Here, the hit comes as individuals face the unique developmental challenges of adolescence, which center on taking on novel social roles and creating new peer relationships, tasks that may uniquely tax BI-linked vulnerabilities (Henderson et al. 2018). Crucially, we anticipate that a two-hit model of the BI–anxiety relation, when reconciled with current formulations, may further clarify why certain children develop anxiety problems, and yet many do not.

This is not an exhaustive review of the BI–anxiety literature. Instead, we briefly describe how BI is expressed across development, why it is related to, yet distinct from, anxiety, and what within-child factors play a role in the etiology of anxiety among children with BI. To foreshadow, converging evidence from cognitive and developmental science suggests that specific patterns of attention and cognitive control potentiate anxiety risk for children with BI (Fox et al. 2021, Henderson & Wilson 2017). After reviewing the evidence for this claim, we then turn to a discussion of when dysfunction in these systems may take root. We emphasize adaptive development during periods when the brain is particularly plastic, namely, in gestation and infancy and again in adolescence. It is here that we make our case in support of a two-hit model of the BI–anxiety relation.

THE BEHAVIORAL INHIBITION–ANXIETY RELATION

The Behavioral Inhibition Phenotype

A young child's temperament reflects a modestly stable pattern of affective reactivity and regulation, rooted in biology, that interacts with environmental influences to shape behavioral development (Shiner et al. 2012). BI is one the most thoroughly examined temperaments (Pérez-Edgar & Fox 2018), due in part to its carefully delineated network of biological systems that can be characterized early in life and captured over time. Young children who are high in BI are often hypervigilant toward novel situations and stimuli. This vigilance appears alongside a constellation of behaviors, including fearfulness, reticence, and negative affect (Fox et al. 2001, Garcia-Coll et al. 1984, Kagan et al. 1984). This pattern of reactivity is a defining feature of BI, although the stimuli that evoke distress tend to move from undifferentiated sensory novelty to social cues as a child ages.

Four-month-olds who respond to novel stimuli with excessive motor agitation and negative affect tend to show high levels of BI by age 2. Replicated in three independent samples (Fox et al. 2015), this profile of negative reactivity may serve as an early appearing indicator of the biological substrates that contribute to later BI (Filippi et al. 2021). From toddlerhood onward, children with BI are often apprehensive in unfamiliar social situations, with many children choosing to actively avoid or withdraw from these encounters (Rubin et al. 2009). Some, but not all, of these children will continue to show this pattern of inhibited behavior into adolescence (Chronis-Tuscano et al. 2009) and adulthood (Tang et al. 2020).

The putative mechanisms that underpin BI are thought to be stable over time, despite changes in behavior. In his foundational work, Jerome Kagan conjectured that the limbic system for children with BI may be exceptionally reactive compared with their less inhibited peers. He specifically pointed to excessive excitability of the amygdala and its associated circuitry as central to the profile of behavioral and autonomic reactivity characteristic of BI (Kagan & Snidman 1991).

Extant evidence supports Kagan's initial speculations, revealing differences in the structure and function of fear circuitry among individuals with a history of BI (Clauss et al. 2014, Filippi et al. 2021, Roy et al. 2014). The initial amygdala-linked findings (Schwartz et al. 2003) broadened across 20 years of research to encompass an integrated, multisystemic network that incorporates cardiac, hormonal, physiological, and neural measures (Fox et al. 2005, Fox et al. 2021). In addition, it has become clear that attention (e.g., Pérez-Edgar et al. 2010) and cognitive control (e.g., Valadez et al. 2022a) play essential roles in the emergence and maintenance of BI. Altogether, current formulations of the BI–anxiety relation emphasize variation in both bottom-up and top-down processing among children with BI (Blackford et al. 2018, Henderson & Wilson 2017). This new emphasis also extends the developmental window for relevant mechanisms well into later stages of development.

Behavioral Inhibition and Anxiety Are Associated yet Distinct Constructs

Critically, young children who show high levels of BI are more likely to struggle with anxiety in childhood and adolescence. The magnitude of the BI–anxiety relation was made clear in a recent meta-analysis from Sandstrom and colleagues (2020). Across 8,836 children from 20 independent samples, BI increased the odds of developing social anxiety disorder almost sixfold and any anxiety disorder close to threefold. BI has also been associated with other mental health concerns, including depression (Caspi et al. 1996) and substance use (Lahat et al. 2012, Williams et al. 2010). However, these links tend to be less reliable compared with the BI–anxiety relation. Thus, a coherent picture emerges: BI has a strong and specific link with anxiety disorders, chiefly social anxiety.

What, then, is the nature of the relation between BI and anxiety? Similarities in developmental course and phenotypic expression blur the conceptual distinction between BI and anxiety (Klein & Mumper 2018, Pérez-Edgar & Guyer 2014). Further complicating the matter is the fact that social anxiety and BI share core characteristics, including avoidance of specific social situations due to intense, excessive, and persistent fear of evaluation. Nevertheless, most children with BI do not develop anxiety disorders (Clauss & Blackford 2012), and many anxious individuals do not have a history of BI. Intervention studies further support this demarcation, showing a decrease in anxiety symptoms, but not BI, after treatment among anxious children with BI (Rapee et al. 2010). Finally, the BI–anxiety link is moderated by factors internal and external to the child (Pérez-Edgar & Fox 2018), suggesting that these phenotypes may arise from distinct etiological processes.

All things considered, extant evidence lends preliminary support for a model in which BI and anxiety are distinct, though related, constructs. It is in this formulation that we see BI play a causal role in the etiology of anxiety, under certain conditions. Conceptually, this model is akin to the diathesis-stress model of psychopathology, wherein a psychiatric disorder is the product of an inherent vulnerability (diathesis) catalyzed by one or more environmental stressors (e.g., Nielsen et al. 2020). BI is itself often characterized as the diathesis in this model. The experience of a stressor then potentiates anxiety risk, thus helping to explain why only a subset of children with BI go on to develop anxiety disorders. For example, children with BI are at increased risk when the diathesis, BI, is expressed in the context of oversolicitous parenting, the stressor (Hudson et al. 2018). For this reason, developmental scientists typically focus on delineating specific aspects of BI and known moderators that account for heterogeneity in clinical outcomes.

Attention and Cognitive Control Modulate Flexible Responding

Heightened attention to novelty, salience, or threat is a core characteristic of BI and may potentiate anxiety risk (Fox et al. 2021, Henderson & Wilson 2017). Enhanced responses to affective information such as threat (fear, anger) is a feature of both BI (Morales et al. 2017, Nozadi et al. 2016, White et al. 2017) and anxiety (Clauss et al. 2022, Valadez et al. 2022b). This affect-biased attention describes a person's tendency to preferentially attend to, and subsequently process, specific salient affective information (Todd et al. 2012). Attention biases rely on activity of interconnected neural circuits that include the amygdala, anterior cingulate cortex, and medial and lateral prefrontal regions (Etkin et al. 2011, Monk et al. 2008, Nomura et al. 2004, Sequeira et al. 2021). Todd and colleagues (2012) proposed that affect-biased attention may emerge early in development, be tuned with age and experience, and act as an adaptive form of early emotion regulation (Morales et al. 2016).

By 7 months of age, infants tend to prioritize fearful faces (Heck et al. 2017, Kataja et al. 2019, Leppänen et al. 2018, Peltola et al. 2009), although perceptual sensitivity to fearful faces may emerge earlier (Safer & Moulson 2020). This fear bias may precede or coincide with emerging fear behaviors (LoBue et al. 2019), possibly guiding the perception of and reaction to emergent challenges. Over time, infants become faster at detecting and less likely to disengage from angry faces (Pérez-Edgar et al. 2017, Xie et al. 2021), culminating in a distinguishable anger bias by age 2 (Reider et al. 2022). This later-emerging anger bias may build upon an infant's budding ability to connect others' negative emotions to their subsequent behavior, beginning between 10 and 14 months of age (Ruba et al. 2020). The early emergence and continual refinement of threat biases equips the preverbal infant with an adaptable attentional repertoire for learning from their environment, even in cases where they lack first-hand experience. By toddlerhood, affective biases privilege incoming information deemed motivationally salient in each context, shaping how a young child perceives and interprets their social environment. Among children with BI, these attention biases may pull attention away from ongoing goal-directed behaviors, such as forming a new friendship.

Fox and colleagues (2021) have argued that cognitive control is essential to understanding why, based on their response to this initial attention capture, some children with BI may be at increased anxiety risk. Cognitive control refers to a set of mental operations that support goal-directed behavior by allowing a child to respond flexibly to changing environmental circumstances and ignore automatic or irrelevant information. In their formulation, responses to an initial attention capture may be divided into automatic (i.e., reactive, stimulus-driven) and planful (i.e., proactive, goal-driven) control (Fox et al. 2021). Deployment of automatic control contributes to the vigilance–avoidance dilemma characteristic of BI. In this case, the child with BI remains fixed on the salient information at the expense of adapting to a dynamic social environment. On the other hand, the child with BI who deploys planful control processes may be able to flexibly reorient their attention to achieve a goal (e.g., navigate peer interactions). Among children with BI, a reliance on automatic control potentiates anxiety risk, whereas planful control protects against anxiety disorder development (Buzzell et al. 2021, Troller-Renfree et al. 2019, Valadez et al. 2021, Valadez et al. 2022a), underscoring the importance of cognitive control to the BI–anxiety relation.

So far, we have discussed the core constructs of BI and anxiety, as well as some of the mechanisms known to modulate their relation, namely, attention and cognitive control. Missing from current formulations is clarity on how these factors come together in a developmental sequence to shape individual outcomes. We turn now to our organizing framework.

A TWO-HIT MODEL OF BEHAVIORAL INHIBITION AND ANXIETY

Two-Hit Models in Developmental Psychopathology

In formulating this review, we borrow our framing analogy from a construct first introduced within the cancer genetics literature. Knudson (1971) introduced a two-hit hypothesis to explain the development of specific forms of cancer. The theory states that two separate events, or hits, are required to cause the disease. The first event is a genetic alteration that occurs in a cell and provides a growth advantage. The second event is a separate alteration that allows the cells to escape normal growth controls. Together, these two hits result in uncontrolled cell division and the development of a tumor. Although emerging from a disparate field of study, we are not the first to borrow this analogy to help explain psychological phenomena.

For example, Picci & Scherf (2014) used the model to help frame a pattern of pubertal deterioration sometimes seen in the autism literature. They argued that the first hit was embedded in early perturbations in neural development that could emerge in fetal or neonatal development. The second hit is triggered by the qualitatively unique surge of hormones in adolescence that are coupled with adolescent-specific social demands. Working with a rodent model, Catuzzi & Beck (2014) examined sex differences in the acquisition of fear responses. In this formulation, females are at increased risk for perturbed fear learning if they show both an attention bias to threat (first hit) and the rodent phenotypic profile of BI (second hit).[1] A human parallel was noted by Sheynin and colleagues (2014). In another rodent model (Davis et al. 2018), chronic pain in the neonatal period is associated with tactile hypersensitivity only if the rodents later experienced a fear-conditioning paradigm. A similar pattern was evident when maternal separation was used as the initial stressor (Chocyk et al. 2014). In each case, mechanisms of interest were linked to modulations in amygdalar maturation and function, creating a conceptual link to the processes evoked when explaining the BI–anxiety relation.

A Two-Hit Model of the Behavioral Inhibition–Anxiety Relation

The two-hit model is not a reformulation of our understanding of the developmental arc between early temperament and later psychopathology. Rather, it complements prior work by viewing available data anew while integrating perspectives often siloed within disparate literatures (e.g., developmental programming, cognitive science, ethology). The strong and specific BI–anxiety link, as reviewed above, lays the conceptual foundation for applying a two-hit model to understanding this relation.

Experiential hits are linked to challenges that emerge as individuals work through developmental milestones that are unique to specific maturational windows. In infancy (including fetal development), the individual is tasked with learning to efficiently decipher a dynamic sensory and inherently social environment that they themselves will enter and, in time, shape. Caregiver distress may communicate the presence of threat or uncertainty in the environment, regardless of whether it is actually present (Kalomiris & Kiel 2016). Infants may internalize this information, tuning attentional systems to prioritize novelty, salience, or threat. Adopting patterns that contribute to the heightened threat-detection ability characteristic of BI may be adaptive in the short-term but thwart the development of flexible behavioral responding (Pérez-Edgar 2018) by rigidly tuning emerging cognitive and affective systems (Gluckman et al. 2007, Todd et al. 2012).

[1] Catuzzi & Beck (2014) center on similar constructs, and variable labels, as the core argument noted here. In their formulation, BI is seen as a hit that increases risk in female rodents. We do not see BI (as defined in human children) as a hit in and of itself. Rather, we consider BI to be a phenotypic indication of an initial hit in either gestation or infancy (**Figure 1**).

In adolescence, the individual is tasked with creating qualitatively new social relations in anticipation of the transition to a more independent young adulthood. This transition is partially triggered by pubertal maturation, carried by neural reorganization, and then embedded within specific social expectations (Sisk & Gee 2022). Importantly, the changes seen in adolescence are not simply the result of accumulating experience or risk. Rather, it reflects a qualitative shift in openness to experience, much as in infancy. Indeed, our argument is in line with accumulating evidence for a pubertal recalibration of multiple systems associated with the stress response and socioemotional functioning (Sisk & Gee 2022). Our proposed two-hit model of the BI–anxiety relation is depicted in **Figure 1**.

First Hit: Gestation and Infancy

The Developmental Origins of Health and Disease hypothesis suggests that experiences beginning in gestation may adaptively tune the structure and function of emergent and malleable biological systems, possibly to prepare the developing fetus for forecasted conditions postnatally (Gluckman et al. 2007). The brain is a likely target for a potent hit in gestation and infancy as it develops most rapidly in utero through the fourth postnatal month (W. Gao et al. 2017, Thomason 2020), followed by a protracted period of elaboration and refinement of functional brain networks (W. Gao et al. 2017, Keller et al. 2023). Functional adaptations may serve to narrow the range of possible phenotypes a fetus or infant may express to better fit anticipated conditions. Crucially, these functional adaptations may come at the expense of health later in development (Padmanabhan et al. 2016). Thus, lifelong consequences in physical and mental health may find their foundations in utero and in the first months of life (Schwab & Rakers 2022).

An initial hit during infancy (or fetal development) may communicate to the developing child that conditions in the environment are uncertain, possibly unsafe. This signal is conveyed to the infant principally through the primary caregiver, directly via uteroplacental mechanisms when in utero (Rakers et al. 2020) or indirectly via emotion socialization mechanisms that tune affect-biased attention in infancy (Todd et al. 2012). While these putative signals may come in multiple forms, we contend that caregiver distress is a potent experiential hit during this specific window of heightened plasticity (Thomason 2020). We consider distress as an umbrella concept that includes multiple negative psychological states, chiefly, perceived stress and anxiety.[2] The net effect of exposure acts as a hit to developing cognitive and affective systems.

The early origins of BI are reflected in the foundational and early maturing brain systems associated with the temperament. Some of the putative neural circuits related to BI are evident and active beginning in the newborn period and may support early differences in detection abilities. For example, stronger amygdala–cingulate resting state functional connectivity in the first month of life has been shown to predict higher infant fear and cognitive development at 6 months and internalizing symptoms at age 2 (Graham et al. 2016, Rogers et al. 2017, Thomas et al. 2019). Neonatal functional connectivity of the ventral attention and default mode networks are associated with BI at age 2 (Sylvester et al. 2018). Amygdala connectivity with the medial prefrontal cortex, ventral striatum, and insula is also related to infant fear (Graham et al. 2016, Rogers et al. 2017, Thomas et al. 2019). By 4 months of age, infants who display more negative affect in response to novelty—an affective precursor of BI (Fox et al. 2015)—show greater amygdala–cingulate connectivity (Filippi et al. 2021). Moreover, BI has been associated with stable and early appearing

[2]Some researchers include depression in their definition of prenatal distress. Although depression often co-occurs with stress and anxiety in pregnancy (Field et al. 2003), we exclude depression from our definition of distress for parsimony.

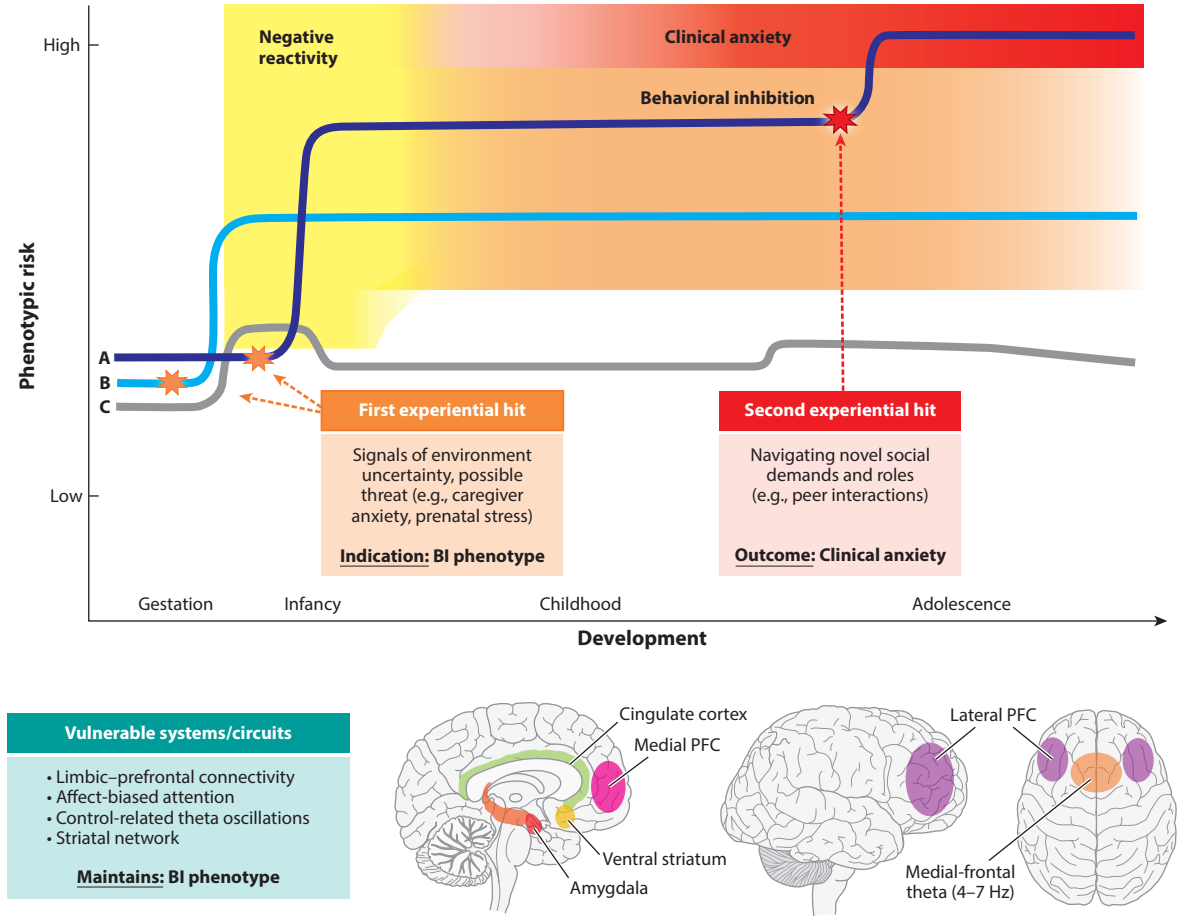

Figure 1

Schematic representation of the two-hit model of the BI–anxiety relation. We depict three hypothetical children and their relative level of phenotypic risk for anxiety, from gestation through adolescence. In this illustrative example, Child A experienced an initial hit in infancy and a subsequent hit in adolescence, following a childhood of expressing the BI phenotype. We contend that this child is most likely to develop an anxiety disorder. Child B, on the other hand, experienced a hit in utero, thereby increasing their relative phenotypic risk. Across development, this child may be more likely to display temperamental reactivity and, ultimately, BI. However, without a second hit this child may never develop an anxiety disorder. Instead, they may develop into a quiet, possibly socially attuned young person who may be better equipped to flexibly navigate their social environment. This example child represents individuals who show stability in BI over time but do not develop an anxiety disorder, possibly due to a proclivity to deploy proactive control (Fox et al. 2021). Child C does not experience any experiential hits across development. This child may follow secular trends related to the rise and fall of negative affect in infancy (Dollar & Calkins 2019) and marked increases in mental health concerns in adolescence (Kessler et al. 2005). However, without the initial hit in early development, this child will not develop an anxiety disorder via the specific BI–anxiety pathway. Key components of implicated neural circuits and systems are presented as well. Abbreviations: BI, behavioral inhibition; PFC, prefrontal cortex.

potentiation in the brainstem auditory response (Geva et al. 2014, Woodward et al. 2001). Once again, a coherent picture emerges: Neural circuits in place in the first weeks of life may support early detection abilities, attention bias development, and fear and novelty processing.

Converging evidence points to the role of prenatal distress on developing brain systems (Dufford et al. 2021), including networks that are pertinent to the BI–anxiety relation. For

example, higher levels of prenatal anxiety are associated with greater neonatal brain responses to novelty in the anterior cingulate, ventrolateral prefrontal cortex, and insula (Sylvester et al. 2021), as well as slower volume growth in the hippocampus through 6 months of age (Qui et al. 2013). Relatedly, higher levels of perceived stress or anxiety while pregnant are associated with modulations in both the functional and structural white matter architecture of the infant brain (Demers et al. 2022, Humphreys et al. 2020, Rifkin-Graboi et al. 2015), centered on regions associated with both BI and general anxiety risk (Rifkin-Graboi et al. 2015, Sylvester et al. 2021). Collectively, exposure to prenatal distress may tune developing neural circuits related to cognitive and affective systems in preparation for an uncertain or variable postnatal environment. To this end, Kataja and colleagues (2019) recently showed that prenatal anxiety predicted greater attention bias to threat among 8-month-old infants, even when accounting for postnatal anxiety. Nevertheless, specific mechanisms through which prenatal distress affects these developing brain systems remain elusive (Braun et al. 2020, Rakers et al. 2020), a critical shortcoming to understanding the intergenerational transmission of psychopathology risk.

In infancy, affect-biased attention is a key target for an experiential hit. Affect-biased attention is evident early in the first year of life (Morales et al. 2016) and may be tuned with age and experience through habitual deployment in response to contextual demands (Todd et al. 2012). The capacity to explore, test new engagement strategies, and learn from the environment relies heavily on social information that is (ideally) robust and reliable (Pérez-Edgar 2018). In infancy, this information is provided principally from the primary caregiver, who may communicate the presence, or possibility, of danger through their affective cues. Infants often prioritize negatively valenced affective information, possibly to gauge if danger is present and, if so, whether it is a direct (angry) or indirect (fearful) threat to their well-being. Tuning early in development would allow the child to quickly learn how to engage novel or uncertain environmental conditions. This information may then be utilized to determine whether it is appropriate to explore for new knowledge or exploit previously successful behavioral repertoires (Pérez-Edgar 2018). At the extreme, caregiver distress, particularly if variable over time (Gunther et al. 2022, Vallorani et al. 2023), may convey unpredictable conditions, signals that the perceptive infant takes in as evidence for an environment signaling caution.

At the group level, attention biases to threat emerge and stabilize (or dissipate; e.g., Leppänen et al. 2018) in the first years of life (Reider et al. 2022). However, at the individual level, attention biases to threat vary across infancy (Dela Cruz et al. 2023, Kataja et al. 2022, Vallorani et al. 2023, Xie et al. 2021), raising questions about factors that contribute to divergent trajectories. We contend that caregiver distress (stress, anxiety) may be one particularly potent factor given the salience of caregiver–infant interactions in early development. Indeed, caregiver anxiety associates concurrently (Kataja et al. 2019, Morales et al. 2017, Vallorani et al. 2021) and longitudinally (Aktar et al. 2019, Vallorani et al. 2023) to infant attention bias to threat. Moreover, infants of parents who reported greater perceived stress show more vigilance to and less disengagement from threat between 4 and 6 months of age (Burris et al. 2022, Reilly et al. 2022), a period when most infants struggle to differentiate negative emotions without additional sensory information (Heck et al. 2017). Also noteworthy, recent findings show that parental affect-biased attention predicts infant affect-biased attention (Aktar et al. 2022).

It is important to note that some studies do not observe a link between caregiver anxiety and affect-biased attention in infancy. Inconsistent findings are often attributed to differences in anxiety severity (e.g., low-to-moderate anxiety; Leppänen et al. 2018) and timing of assessment (e.g., Burris et al. 2022), or a combination of the two. Less often examined is the stability of caregiver anxiety across infancy, despite it being a potentially salient indicator of uncertain environmental conditions. To this end, Vallorani and colleagues (2023) found that infants whose mothers reported

more fluctuating anxiety levels showed a stable pattern of affect-biased attention over time. This effect was specific to fluctuations in caregiver anxiety during the second year of life (Vallorani et al. 2023), a period defined by marked increases in motor abilities and autonomy when an infant may rely on their caregiver for guidance about safety (Aktar & Pérez-Edgar 2020).

Altogether, we contend that a hit in the form of caregiver distress to BI-relevant systems during gestation or infancy may set foundational attentional and affective patterns, which may then canalize as this early sensitive period comes to a close. We speculate that neural circuits that support the detection of salient (novel, threatening) information in gestation and affect-biased attention mechanisms in infancy are likely targets of these hits given their plasticity and relative openness to tuning on the basis of experience (Gluckman et al. 2007, Todd et al. 2012). In this case, it may be advantageous to crystallize currently successful patterns of responding in less predictable conditions (e.g., Vallorani et al. 2023), even if this rigidity affords less reward over time or across contexts. Indeed, this adaptive trade-off is thought to come at the expense of testing new strategies of engagement, which may be initially riskier but could afford greater reward later (Pérez-Edgar 2018). This includes learning to flexibly adjust one's behavior to novel social challenges, a hallmark shortcoming among children with BI (Henderson et al. 2018). The type and timing of experiences that constitute threat signals may differ but still contribute to the vulnerable pattern of cognition, affect, and behavior characteristic of BI in childhood. The implicated neural systems and circuits also contribute to the manifest BI phenotype across childhood. Importantly, the initial hit leaves these neural circuits and systems vulnerable to a second hit during a subsequent period of heightened plasticity.

Second Hit: Adolescence

Adolescence is marked by a distinct shift in social relationships. Peer interactions become more salient, changing in relevance for socioemotional development relative to younger ages. This leads to an increased motivation to master new peer-oriented interactions, with new skill development in face processing and emotion identification supporting this goal (Scherf et al. 2012). At a global level, the social reorientation of adolescence is characterized by a movement away from familial bonds to peer relationships, often in anticipation of creating independent, long-term, and potentially romantic relationships (Crone et al. 2022). Within peer relationships, we also see qualitative changes in the quantity, quality, and nature of these relations—again in anticipation of forming smaller, longer-lasting, and more intimate bonds. Adolescence is also marked by qualitative changes in self-concept and appraisal (Crone et al. 2022). Often, the literature characterizes these changes as a moment of risk since normative or secular trends capture marked increases in mental health concerns in adolescence (Kessler et al. 2005).

However, of importance to the current formulation, maladaptation in adolescence is not simply reflecting linearly accumulated risk. Rather, adolescence is a distinct developmental period of newly emerging opportunity for recalibration and change (Fuhrmann et al. 2015, Sisk & Gee 2022). For some children, this moment of recalibration can help rectify early difficulties (Gunnar et al. 2019). For example, previously institutionalized children show perturbed stress responses, indexed by hypothalamus-pituitary-adrenal axis reactivity to a social evaluation task. Adoption into enriching and supportive families does not appear to rectify this perturbation until the transition into peripuberty. Longitudinal work from Gunnar and colleagues (2019) found that previously institutionalized adolescents recalibrate and begin to match cortisol patterns in never-institutionalized peers in a systematic fashion as they move through phases of pubertal development. Importantly, this is a within-subjects phenomenon in that recalibration emerges as an idiosyncratic marker of pubertal transition and is not captured by average, or between-subjects, differences in puberty at any one age (Gunnar et al. 2019). This work exemplifies the importance

of adolescence (and puberty) in reopening a window of opportunity for the recalibration of a stress-mediated system.

In our formulation, we focus on BI-relevant cognitive and affective systems that were made vulnerable from an initial hit in infancy as they enter periods of possible recalibration in response to changing social dynamics. BI is associated with less flexibility in exploring the environment, which is a critical learning process in the transition from childhood to young adulthood. Exploration offers more learning experiences and helps the individual gain new adaptive skills that can be applied to a wider range of social settings. To borrow a term from ethology, Adolescents with BI are more likely to exploit the environment rather than explore it (Pérez-Edgar 2018). That is, they rely on prior learned skills and knowledge, limit the scope of environments in which these skills will be tasked, and, when finding themselves in novel environments or facing novel social challenges, will rigidly deploy prior responses. This is in contrast to the normative pattern of increased exploration in adolescence that then settles into greater exploitation—placid adult domesticity, if you will. Support for this idea comes from the literature on cognitive control.

Cognitive control matures into adolescence (Luna et al. 2015). Anxiety risk for children with BI is moderated by proactive control development that occurs across adolescence (Troller-Renfree et al. 2019, Valadez et al. 2021), with greater proactive control buffering adolescents with BI against age-related increases in anxiety (Valadez et al. 2022a). Unique organizing properties of reactive and proactive control may be indexed by theta oscillation (4–8 Hz) dynamics (Cavanagh & Frank 2014). For example, error monitoring and control recruitment may be reflected in theta power over the midline frontal cortex and theta connectivity between medial and lateral frontal cortices, respectively (Cavanagh & Frank 2014, Ullsperger et al. 2014). Theta dynamics associated with cognitive control are present in early adolescence before increasing to adult-like levels soon after (Buzzell et al. 2019, Hwang et al. 2010).

Notably, control-related theta dynamics may be tuned in mid-to-late adolescence by social observation and motivation (Buzzell et al. 2019, Crowley et al. 2014). Social observation, specifically in adolescence, affects motivation (Nelson et al. 2016), which may influence how an adolescent deploys cognitive control strategies. To this end, Buzzell and colleagues (2019) found that peer observation upregulated theta measures related to postresponse error monitoring (medial frontal cortex theta power) and proactive control (connectivity of medial–lateral frontal cortices) in adolescence. Along with medial frontal cortex theta synchrony, postresponse medial frontal cortex theta power serves as an alarm signal that recruits from the lateral frontal cortex to instantiate top-down control in response to errors or conflicts (Cavanagh & Frank 2014). This finding supports the idea that there is a period for calibration of cognitive control systems before transitioning into young adulthood that is acutely sensitive to the social environment (Crowley et al. 2014), a context which may uniquely tax BI-linked vulnerabilities.

Despite improving cognitive control abilities, heightened reactivity of the limbic system in adolescence may exert a disproportionate influence on adolescent motivation (Casey et al. 2008, Luciana & Collins 2012, Nelson et al. 2016). Subcortical development, which is often associated with fear and reward processes of interest in BI, may be more variable in adolescence than cortical development and partially driven by pubertal processes (Goddings et al. 2014, Wieringa et al. 2018). This pattern of social sensitivity is associated with a distributed neural network that extends beyond the original amygdala model of BI. For example, the striatal network is associated with reward processing, decision-making, habit formation, and motor control. Centered on the caudate, putamen, and nucleus accumbens, the network is highly connected to the prefrontal cortex, the amygdala, and the hippocampus (Guyer et al. 2006, Nelson et al. 2016). Puberty-related maturation of frontostriatal functional connectivity has been linked to inhibitory control development (Ojha et al. 2022).

Initial studies with children with BI examining striatum-linked processes assumed that they would express less activation as a counterbalance to the hyperreactive response to threat or salience in the limbic system. However, across two well-validated reward tasks, children with BI expressed greater activity to monetary reward compared with their noninhibited peers (Bar-Haim et al. 2009, Guyer et al. 2006, Pérez-Edgar et al. 2014). This pattern was further probed by manipulating the contingency between reward and child performance (Helfinstein et al. 2011). That is, in some trials the adolescents received a reward regardless of performance. In other trials, reward was provided only when the adolescent provided a correct response. It was only in this second condition that adolescents with BI showed increased striatal activity relative to noninhibited peers. These data suggest that adolescents with BI are not sensitive to reward per se. Rather, they are sensitive to external cues that they can use to make self-assessments or engage in self-monitoring, a core task in adolescence (Crone et al. 2022) that is potentiated in BI. Analogously, social cues (e.g., smiling faces) provide these adolescents with feedback they can use to judge their social performance.

Adolescence is a distinct developmental period of newly emerging opportunity for the recalibration of affective and cognitive control systems (Fuhrmann et al. 2015, Sisk & Gee 2022), often motivated by maturing peer dynamics (Scherf et al. 2012). In our formulation, we contend that BI-linked vulnerabilities, implicated due to distress-related experiences in early life (first hit), may be exacerbated by the unique salience of changing peer relationship dynamics in adolescence (second hit), increasing the likelihood that the adolescent will develop an anxiety disorder. It is through this path that we contend BI and anxiety are linked (see **Figure 1**).

CAVEATS AND CONSIDERATIONS

Several caveats are needed when weighing the validity of our formulation for the BI–anxiety relation. First, this perspective is probabilistic, not deterministic. That is, among children with BI, the likelihood of developing an anxiety disorder increases following a second hit in adolescence, but a second hit does not guarantee a disorder will manifest. This argument echoes the idea that BI limits the range of possible phenotypes a child may express but does not determine who a child will be (Kagan 2018).

Second, evidence indicates a transactional association between BI and known moderators, such as parenting, in shaping anxiety risk (e.g., Kalomiris & Kiel 2016). While not explicitly noted in our model, we view transactional processes as embedded in the day-to-day interactions between a caregiver and their child that tune early attentional biases and cognitive processes. This process is similarly observed in peer interactions for adolescents with BI, shaping the recalibration of socially oriented cognitive and affective systems. While we do recognize the importance of transactional interactions with caregivers and peers during childhood, we contend that these interactions do not tax vulnerable circuits and systems to the same degree, or in the same qualitatively distinct manner, as in infancy (including fetal development) and adolescence.

Third, this is not the only path to anxiety. Rather, our formulation is meant as an organizing framework for a group of children who are at enhanced anxiety risk due to their temperament, leveraging knowledge on sensitive periods of brain development and developmental programming. It is possible that unique mechanisms may account for anxiety difficulties among children with and without BI. For example, caregiver emotion modeling of distress may be one mechanism for anxiety transmission for all children, not only those children with high levels of BI (Perlman et al. 2022). Whether the type or timing of certain experiences leads to anxiety problems differently on the basis of BI status in childhood warrants investigation.

Lastly, the perceptive reader will notice our deliberate omission of genetics from the current formulation. Genetic predisposition is a common hit in two-hit models, reflecting extensive

research into (poly)genetic contributions to a specific disorder (e.g., schizophrenia; Maynard et al. 2001). Despite twin studies suggesting moderate heritability (Smith et al. 2012), and some candidate gene studies identifying implicated variants (e.g., Smoller et al. 2003), the search for the genetic contributions to BI has been long and disappointing. It is for this reason that we do not specify a role of genetics in our two-hit model. Still, genes related to dopamine signaling have been linked to anxiety disorders and symptoms (e.g., Nikolaus et al. 2010) and may play a moderating role in the BI–anxiety relation (Pérez-Edgar et al. 2014) by influencing executive functions and reward processing (Gunther & Pérez-Edgar 2021). Future iterations of the proposed two-hit model may include genetic predisposition as a hit depending on how this line of research matures in regard to the BI–anxiety relation.

FUTURE DIRECTIONS

In 2005, Fox and colleagues (2005) wrote a comprehensive assessment of BI, distilling nearly 20 years of systematic study into a coherent developmental framework. The current review now looks back at a scientific endeavor at the cusp of 40 years of work. Below, we present a few outstanding issues to further clarify the BI–anxiety relation.

Specificity of Experiential Hits

It is worth noting that some hits, such as caregiver distress exposure in utero or social evaluation in adolescence, may exert influence on several interconnected circuits and systems. The question then becomes, are the proposed hits specific to the BI–anxiety relation or do they confer general psychopathology risk? Although BI-linked vulnerabilities are well documented (Pérez-Edgar & Fox 2018), it remains an open question as to whether (*a*) specific hits that occur during (*b*) discrete time windows and (*c*) speak to distinct developmental challenges account for the BI–anxiety relation, as we propose here. Determining the specificity of these hits to specific (BI) versus general psychopathology risk may inform future prevention efforts.

We consider our definition of distress (perceived stress, anxiety) as a starting point, meant to draw a clear conceptual link between exposures in utero, experiences in infancy, the BI phenotype, and BI-linked cognitive and affective systems. That said, other forms of stress or mental health concerns may also be relevant as experiential hits (Dufford et al. 2021). For example, Spann and colleagues (2022) found that infants of young, predominantly Hispanic/Latina women who experienced discrimination while pregnant showed weaker amygdala–prefrontal connectivity. Moreover, Qiu and colleagues (2015) found that 6-month-olds whose mothers reported higher levels of depressive symptoms while pregnant showed greater functional connectivity between the left amygdala and brain regions related to emotion regulation (e.g., anterior cingulate, orbitofrontal cortex). Future iterations of this proposed model may benefit from an expanded definition of caregiver distress. Clarifying the mechanisms linking prenatal emotional experiences to BI-linked vulnerabilities may also inform how we operationalize distress prenatally. Unfortunately, support for specific mechanisms that link prenatal distress to infant outcomes remains elusive (Dufford et al. 2021).

Context and Culture

The BI literature is dominated by studies carried out within the United States. Within the US, the populations studied have been overwhelmingly white, highly educated, and solidly middle class (Chronis-Tuscano et al. 2022). In this context, the literature has produced a robust picture of the types of risk faced by children with BI. However, cross-cultural work suggests that BI does not predict a universal risk profile. For example, children in China with early signs of BI were later

rated by teachers as having stronger social relationships, better academic outcomes, and fewer signs of psychopathology. A decade later, this profile held for children with BI in rural China. However, for urban children, BI was a risk factor for maladaptation, much as in the United States (see Chen 2018, Chen et al. 2021).

It seems unlikely that the mechanisms that first led to the emergence of BI shifted over time in China or varied between China and the United States. In contrast, parental reports of temperament do seem to reflect variations in cultural expectations early in life. For example, a recent pooling of temperament questionnaire data from 59 countries (S.P. Putnam, manuscript under review) found that ratings of negative affect and surgency consistently varied across south and southeast Asia, South America, and northern and western Europe. These ratings likely reflect culturally mediated expectations for normative and ideal temperamental profiles. With respect to BI, variation in culturally mediated external responses and subsequent changes in self-evaluation may create a qualitatively different developmental context as children enter adolescence given that social reorientation away from parents and toward peers is of course culturally mediated (Arnett 2011). Thus, applying a two-hit model in these circumstances could help researchers better understand diverging developmental pathways. In the same way, emerging data suggest that anxiety-like behavior can be protective for children growing up in risky environments if it removes them from instances of potential harm (Ellis et al. 2017). Again, this instance of contextual variation could help refine the boundaries and robustness of this model.

Cortical Excitation/Inhibition Balance

Going forward, it may be useful to explicitly integrate excitation/inhibition (E/I) balance dynamics into models of BI, development, and psychopathology risk. The E/I balance captures the relative contribution of excitatory (predominantly glutamatergic) and inhibitory (predominantly GABAergic) synaptic currents to brain signaling (Froemke 2015, R. Gao et al. 2017). Effective information processing, from local neuronal circuits to whole-brain networks, depends on the integration of these synaptic inputs. The E/I balance contributes to initiating a sensitive period (Takesian & Hensch 2013, Zhang et al. 2011) and is susceptible to stress in gestation (Marchisella et al. 2021) and adolescence (Wang et al. 2019). New techniques for noninvasive assessment of the E/I balance offer novel insights into development and psychopathology (Chini et al. 2022, Donoghue et al. 2020, Larsen et al. 2022, Leno et al. 2022), shedding new light on prior formulations. For example, Howes & Shatalina (2022) recently outlined the role of E/I imbalance in the prefrontal cortex in the etiology of schizophrenia, reconciling two prominent theories of the disorder. Novel formulations such as this may help integrate research on dopaminergic activity and anxiety risk among children with BI (Gunther & Pérez-Edgar 2021) into the proposed model. The role of cortical E/I balance for BI-linked vulnerabilities warrants investigation.

CONCLUSIONS

In the 1920s silent film *One Week* (Keaton & Cline 1920), a newlywed couple (played by Sybil Seely and Buster Keaton) attempts to construct a new build-it-yourself kit home[3] in the seven days leading up to a housewarming party. Their plans are thwarted when, unbeknownst to them, a rejected suitor maliciously tampers with their assembly instructions. Although functionally (and aesthetically) odd in some ways (e.g., lopsided structure, revolving walls, exterior-leading second floor door), the couple ultimately creates a home that serves their purpose. It is not until a storm

[3]The build-it-yourself kit home was a relatively common option for new homeownership in the United States in the 1920s, a fact the first author recently learned and shares ad nauseam.

hits (on the day of the housewarming party, no less) that foundational vulnerabilities of the home become evident and proliferate—the storm sends the house and its occupants revolving like a merry-go-round. Although mishaps for the newlyweds continue, this story arc provides an apt analogy for our conceptualization of a two-hit model. That is, it is not until a second hit occurs (the storm) that the effects of the initial hit (the tampered building plans) come into full view. In isolation, neither of these experiential hits would result in the ruinous final outcome, although daily life may not necessarily be enjoyable with a structurally lopsided home. But in combination, these hits send the house and its occupants spinning, elevating into problematic home behavior.

In this review, we have evoked a number of core models in developmental science to better understand the plainly evident relation between BI and anxiety. Diathesis-stress models, for example, have been critical in understanding temperament-linked psychopathology risk but are limited in scope to one aspect of a multidimensional and probabilistic developmental chain. In supplementing this approach with a two-hit model, we move the focus of attention to specific developmental challenges that are tied to distinct maturational windows when the brain is particularly plastic (Gabard-Durnam & McLaughlin 2020), that is, in gestation and infancy and again in adolescence. The links between infant and adolescent experiences are not random or interchangeable with other developmental periods. Rather, the connections noted here reflect yoked developmental processes or mechanisms that are centered on the biological response to social context and environmental input. Shifts in the time windows examined, or analyses that focus solely on the accumulation of risk over time irrespective of timing, may not provide the same unique pattern of observed adaptation and maladaptation.

In our proposition, the two-hit model helps explain patterns of responses that speak to the idiosyncratic concerns of BI coupled with normative developmental processes potentiated in infancy and adolescence. In this work we are keen to increase our specificity when discussing the developmentally mediated mechanisms and profiles that help us better understand BI as a temperament and as an antecedent to later developmental outcomes. For example, we currently lack a sensitive measure of reactivity and BI in adults. In line with Kagan's (2018) formulation, we suggest that this is a feature, not a bug. That is, the specific biological and experiential mechanisms that modulate the emergence and trajectory of BI are, by definition, bound to specific developmental windows in which normative and risk processes interact in an emergent manner to shape outcomes. In moving beyond early childhood, we looked to see how BI was associated with, or led to, the emergence of anxiety in adolescence. We are not examining patterns of BI in adolescence. Because BI is not simply a prodrome of anxiety (Pérez-Edgar & Guyer 2014), and there are qualitative shifts in how we define adaptive behavior, questions of BI continuity or discontinuity lose their practical utility at some point. In this vein, groundbreaking longitudinal studies have outlined how early BI, coupled with adolescent experience, shapes functioning well into adulthood (Tang et al. 2020). Thus, the current two-hit model provides a framework for study that is both mechanistically broad and time limited.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENTS

We thank our team at the Cognition, Affect, and Temperament Laboratory for thoughtful discussions pertinent to this review. We are grateful to the many families who dedicated their time to participate in studies that informed the ideas raised here. This review was supported by the

National Institute of Mental Health under awards K99MH126791 (to B.O.) and R01MH109692 (to K.P-E.).

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