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SYSTEMATIC REVIEW

Developmental Pathways from Early Behavioral Inhibition to Later Anxiety: An Integrative Review of Developmental Psychopathology Research and Translational Implications

Pan Liu[1] · **Koraly E. Pérez-Edgar**[2]

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Abstract
Anxiety is among the most prevalent, early emerging, and detrimental mental conditions for children and adolescents. As with most psychiatric disorders, prevention and intervention efforts are most effective when the early etiology of the disorder is well understood from a developmental perspective. To illustrate this point, this article reviews the developmental psychopathology research in youth anxiety, with a focus on a prominent temperamental risk for anxiety, behavioral inhibition. This review underscores three systems that may act as mechanisms with behavioral inhibition in conferring risks for anxiety: neural, cognitive, and environmental. Based on findings from these systems, a developmental model is proposed to illustrate the multi-determined pathways from early behavioral inhibition to anxiety, which often is most acute in adolescence. This article further discusses several translational directions for developing targeted prevention/intervention tools. As emphasized in this review, understanding the early mechanisms of youth anxiety can help health practitioners target specific constructs that predispose individuals at risk, capturing developmental time windows that are more malleable for prevention/intervention, and identify bio-behavioral indicators that predict illness trajectories and treatment effects. This article provides an integrative summary of the literature and sheds light on future work of both mechanistic investigations and clinical practices for anxiety in youth and adolescents.

Keywords Anxiety · Childhood · Adolescence · Behavioral inhibition · Prevention · Intervention

Introduction

Anxiety disorders are among the most prevalent and earliest emerging mental health conditions in the general population. Anxious behaviors may be evident in children as young as age 3 (Egger and Angold 2006). By adolescence, the occurrance of anxiety symptoms significantly proliferates, and the lifetime prevalence rate of impairing anxiety disorders during adolescence approximates 8.3% (Merikangas et al. 2010). If not treated, adolescence anxiety may may persist into adulthood and lead to multi-fold increases in risk for long-term adverse outcomes, including anxiety, depression, and substance abuse (Pine et al. 1998). Therefore, studying anxiety disorders from a developmental psychopathology perspective is critical for better understanding the early (and potentially etiological) factors and processes by which anxiety disorders initiate, perpetuate, and remit. Understanding the early mechanisms of disorder may also aid clinicians in identifying bio-behavioral indicators that predict illness trajectories, targeting specific processes and time windows that are more malleable for prevention and intervention.

This article reviews the up-to-date evidence on the early mechanisms of youth and adolescence anxiety generated by developmental psychopathology research. It will also discuss how this evidence informs the prediction, prevention, and intervention of youth's anxiety problems in both clinical and non-clinical contexts. Among the various etiological factors, this review focuses on one temperamental factor, behavioral inhibition, given data suggesting that it is the strongest individual difference factor in predicting children

✉ Pan Liu
pliu261@gmail.com

[1] Department of Psychology, Brain and Mind Institute, University of Western Ontario, 2172 Western Interdiscplinary Research Building, London, ON N6A5B7, Canada

[2] Department of Psychology, Child Study Center, The Pennsylvania State University, 270 Moore Building, University Park, PA 16802, USA

and adolescent's anxiety problems (Fox and Pine 2012). Behavioral inhibition is an early appearing, biologically-based temperamental trait that is marked by hyper-vigilance and sensitivity to novelty, and is linked to the later emergence of psychopathology, specifically anxiety (Pérez-Edgar and Guyer 2014).

While behavioral inhibition significantly predicts the later emergence of anxiety, not all individuals with early behavioral inhibition become anxious. As suggested by the literature, a number of factors, both endogenous and exogenous to the individual, may come into play at various points through development and moderate (or possibly mediate) the relations between behavioral inhibition and later anxiety. These observations converge with the central tenet of developmental psychopathology, which emphasizes that a particular risk factor, such as behavioral inhibition, may pull the individual onto different pathways toward multiple outcomes (multifinality), and that the targeted outcome can result from a variety of predisposing pathways (equifinality; Cicchetti and Rogosch 1996). To study these pathways, it is critical to step away from traditional, symptom-based diagnostic categories and instead examine the underlying mechanisms that affect the wholistic, continuous spectrum of socioemotional behaviors observed in individuals, ranging from typical and adaptive to atypical and maladaptive. In particular, examining healthy yet at-risk individuals rather than clinical patients is important. While focusing on behavioral inhibition as a primary risk factor for anxiety, this review will also encompass factors drawn from different systems (neurobiological, cognitive, and environmental) and discuss how they interplay with behavioral inhibition in shaping the multiple pathways toward, or away from, later anxiety. Based on the discussion, an abridged conceptual developmental model will be proposed to integrate the different processes in determining the behavioral inhibition-to-anxiety pathways (Fig. 1). Last, the translational implications will be discussed. This will point to several avenues for developing targeted prevention and intervention strategies for anxiety-prone children and adolescents.

Behavioral Inhibition as an Early Appearing Temperamental Trait

As a distinct category of temperament, behavioral inhibition was first characterized by Jerome Kagan (Kagan et al. 1984) as a set of biologically-based, early-appearing, observable behavioral patterns marked by heightened vigilance, sensitivity, fear, and withdrawal in response to novel stimuli in the enviorment, particularly if social in nature (Kagan et al. 2001). These behavioral patterns are also presumed to be relatively stable across contexts and developmental stages. As early as the first months of life, the behavioral

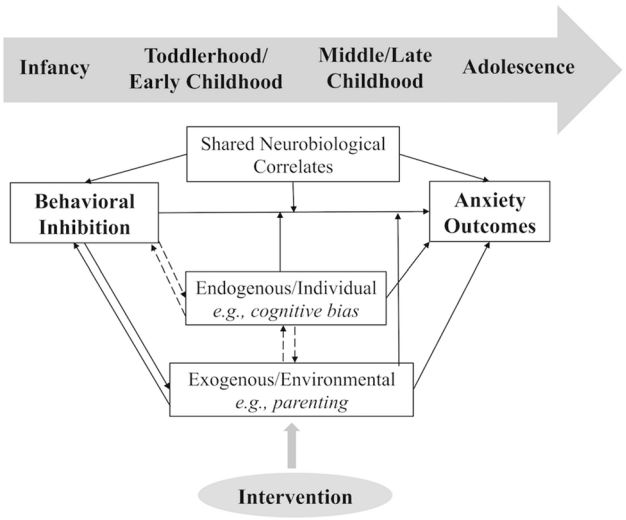

Fig. 1 An abridged developmental model of the potential developmental mechanisms linking early behavioral inhibition to later anxiety outcomes

antecedents of behavioral inhibition are observable in the form of infants' negative reactivity, such as negative vocalizations and vigorous limb movements when presented with benign but novel stimuli (Kagan 2012).

Longitudinal data indicate that negative reactivity during infancy predicts the later presence of behavioral inhibition during toddlerhood (Fox et al. 2001). Behavioral inhibition first becomes identifiable as a set of distinct behavioral patterns in response to novel situations around the second and third years of life. This timing may reflect the fact that this developmental window provides children with the behavioral repertoire necessary to display a full range of individuated responses, but not the regulatory processes needed to modulate their initial reactivity (Kagan 2012). Longitudinal studies have demonstrated moderate stability of behavioral inhibition, with correlations of 0.24–0.64, from toddlerhood through middle childhood, adolescence, and early adulthood (Pérez-Edgar and Guyer 2014).

Behavioral inhibition is also associated with a distinct profile of neurobiological underpinnings. Kagan drew on a line of animal research noting that the amygdala is functional shortly after birth and is linked to the acquisition of conditioned fear, the modulation of distress cries and limb movements. Therefore, he proposed that the unique patterns of behavior observed in negatively reactive infants, which often precedes toddlerhood behavioral inhibition, was a direct reflection of a hyper-reactive amygdala responding to novel stimuli (Kagan 2012). The hyper-reactive amygdala then triggers the distinct behavioral and psychophysiological profiles noted in behavioral inhibition. Indeed, more recent imaging work suggests that the amygdala is a critical, hub-like brain structure within a distributed network

that subserves social and emotion-related processes across development (Scherf et al. 2013). Amygdala function and related behavioral and neurobiological profiles, as discussed below, may also serve as the foundation for the association between early behavioral inhibition and the later emergence of anxiety.

Behavioral Inhibition is Associated with Increased Risk for Anxiety

The initial studies of behavioral inhibition were motivated by the empirical observation that a subset of young children display a distinct pattern of behaviors when confronted with novelty. The interest in anxiety emerged over time as longitudinal data revealed clear links between early behavioral inhibition and later anxiety, particularly in adolescence (Fox and Pine 2012). Thus, from a developmental psychopathology framework, the initial clues to the importance of behavioral inhibition for anxiety came from the careful consideration of emergent developmental trajectories. As a result, subsequent research has aimed to document and explain why, and for whom, this trajectory holds.

As behaviorally inhibited toddlers grow up, many show increasing levels of fear when facing unfamiliar circumstances, social withdrawal, and poorly regulated social behaviors. This pattern of social development may pull some inhibited children onto a trajectory toward later social anxiety (Fox and Pine 2012). In prospective research, early behavioral inhibition emerges as the strongest predictor of risk for later anxiety during late childhood and adolescence, particularly for individuals who show more consistent patterns of behavioral inhibition over time (Biederman et al. 1993). Across studies, this relation is strongest for social anxiety, as opposed to specific phobias and generalized anxiety disorder (Fox and Pine 2012; Pérez-Edgar and Guyer 2014). For instance, Kagan and Snidman (2001) found that at age 13, 61% of adolescents identified as behavioral inhibition at 2-year-old showed signs of social anxiety when interacting with an unfamiliar adult. In contrast, only 27% of their non-inhibited peers show similar anxious behaviors. In another sample, children with high, stable levels of behavioral inhibition from 14 months through 7 years show a fourfold increase in anxiety by mid-adolescence, evident in diagnostic interviews as well as parent- and self-report anxiety symptoms (Chronis-Tuscano et al. 2009). In a meta-analysis of the behavioral inhibition-anxiety association, Clauss and Blackford (2012) found that compared to their non-inhibited counterparts, individuals with high behavioral inhibition during toddlerhood and early childhood show an adjusted odds ratio of 7.59, or a relative risk of 4.12, for developing social anxiety from middle childhood to adolescence.

Mechenisms Explaining Links between Behavioral Inhibition and Anxiety

As prospective data demonstrated the predictive validity of early behavioral inhibition for the later anxiety, researchers started to investigate the mechanisms that could tie behavioral inhibition to anxiety. A series of studies documented patterns of neurocognitive functions in individuals with early behavioral inhibition that parallel observations from clinically anxious individuals, even when the inhibited individuals did not present with a clinical disorder (see review Pérez-Edgar and Guyer 2014). These shared patterns of functioning might identify at least a subset of etiological mechanisms for anxiety in general, and youth anxiety in particular.

On the other hand, not all individuals starting with similar profiles of behavioral inhibition become anxious (multifinality), and one early temperamental risk cannot on its own determine individuals' developmental trajectory toward or away from the maladaptive outcomes. Very few mechanisms of interest can boast that level of determinism. For example, one of the best understood mechanisms of intellectual disability, Down's Syndrome, can be traced to a specific marker—Trisomy 21 (Patterson 2009). And yet, the tell-tale karyotype can tell little regarding that individual's eventual intellectual capacity, socioemotional profile, or level of daily functioning (Sigman et al. 1999). There are simply too many intervening forces, both internal and external to the individual, to allow for anything more specific than broad ranges of description. Behavioral inhibition, with its less determinant biological substrate, and relatively greater sensitivity to experience and context, is surely even more open to variation and fluctuation over the course of development.

This section of the review is circumspect in discussing how the shared correlates between behavioral inhibition and anxiety, as well as the interrelations between behavioral inhibition and other developmental factors, may function as mechanisms that underlie the behavioral inhibition-to-anxiety pathway. As such, this review systematically approaches two important questions for both developmental research and clinical practice: (1) Given early signs of risk (in this case behavioral inhibition), which subset of these young children should be most worried about for the later anxiety? (2) Once identified, what are the specific processes that push these children toward anxiety, and therefore could act as an intervention target to prevent anxiety? Given the extensive work that has been done and the limited space, the current review is by no means exhaustive. Rather, this article draws upon three systems that are relatively prominent and well-studied (neural, cognitive, and environmental) and focuses on specific examples for

each of them: EEG asymmetry and fMRI, attentional bias, and parenting behaviors. Finally, a developmental model is proposed to summarize the extant findings and integrate the processes from different systems, with the aim of providing an abridged conceptual delineation of the various potential pathways from behavioral inhibition to anxiety.

Neural Correlates

As noted earlier, the initially hypothesized neural foundation for behavioral inhibition, drawn from the animal literature, centers on a hyper-reactive amygdala response when confronted with novelty and uncertainty in the environment. However, the first two decades of work progressed without directly examining this brain structure (Schwartz and Rauch 2004), due to the limited accessibility of neuroimaging technologies such as functional magnetic resonance imaging (fMRI). Earlier work exploring the neural correlates of behavioral inhibition used more accessible psychophysiological measures, such as the electroencephalogram (EEG) and event-related potentials (ERP), hypothesized to relate to, or grow out of, the hypersensitive amygdala function (White et al. 2012). For example, behaviorally inhibited children exhibit heightened vigilance to novelty (Reeb-Sutherland et al. 2009) and behavioral errors (McDermott et al. 2008), as reflected in ERP components. The present article focuses on studies of frontal EEG asymmetry in behaviorally inhibited children and then turns to the emerging fMRI literature.

Early inhibited behaviors are associated with greater right frontal EEG asymmetry. This asymmetry is usually quantified as a difference score of alpha band activity between the right and left frontal regions. Right frontal EEG asymmetry is typically associated with withdrawal tendencies, while left front EEG asymmetry is associated with approach motivations (Davidson 2004). Both negatively reactive infants and young children characterized with behavioral inhibition show greater right frontal EEG activity at rest (Hane et al. 2008; Finman et al. 1989). A similar profile was also observed when behaviorally inhibited 4-year-olds performed tasks designed to evoke fearful and withdrawal responses (Theall-Honey et al. 2006). Prospectively, right frontal EEG asymmetry at 9 months is associated with the stability in inhibited behaviors from infancy to 4 years of age (Fox et al. 2001). For children with high behavioral inhibition, stability in right frontal EEG asymmetry from 3 to 10 years accounted for stability in their inhibited behavioral profiles (Davidson and Rickman 1999).

Kagan suggested that greater right frontal EEG activity observed in behaviorally inhibited children might reflect ipsilateral projections from the right amygdala, which was presumed to receive greater bodily inputs than the left amygdala (Kagan 2002). Therefore, when inhibited children showed heightened visceral responses to novel events, their right amygdala became more activated, and in turn resulted in greater activity in the right frontal regions. More recent studies using source modeling techniques suggest that the observed frontal EEG asymmetry is located in, and therefore most directly reflects, dorsolateral prefrontal cortex (dlPFC) activity (Shackman et al. 2009). The functional lateralization of dlPFC has also been supported by imaging evidence, suggesting that the left dlPFC was involved in approach-related, goal-attaining processes and right dlPFC in withdrawal-related behaviors (Spielberg et al. 2008). Activation of right dlPFC during withdrawal-related processes might further support threat-related vigilance (Davidson 2004).

Interestingly, greater right frontal EEG activity has been repeatedly observed in clinically anxious and depressed individuals (Thibodeau et al. 2006). This pattern is also evident in individuals at risk for disorders but without clinical diagnosis, as in offspring of depressed mothers (Field et al. 2009). These data suggest that greater right frontal EEG asymmetry appears to be a shared neural correlate between behavioral inhibition and anxiety, or internalizing problems more generally, and may contribute to tethering early behavioral inhibition and later anxiety.

As fMRI technology has become increasingly accessible, the more recent literature has directly examined the hypothesized amygdala-based neural foundation of behavioral inhibition, documenting overlapping neural underpinnings between behavioral inhibition and anxiety. The first major fMRI study examining the function of amygdala in the context of behavioral inhibition found that young adults identified as behaviorally inhibited in the second year of life displayed exaggerated bilateral amygdala activation to the presentation of novel faces, relative to their peers without a history of behavioral inhibition (Schwartz et al. 2003). Other fMRI studies also observed atypical amygdala activation in young adults characterized with early behavioral inhibition in response to novel faces, including faster latency (Blackford et al. 2011) and failure to habituate to repeated faces (Blackford et al. 2013). Twelve-year-old adolescents characterized as behaviorally inhibited as young children were presented with emotional faces and asked to either passively view the faces or rate their subjective sense of fear. The behaviorally inhibited adolescents displayed greater amygdala activation than their peers without behavioral inhibition only when they had to subjectively rate their internal feelings of fear (Pérez-Edgar et al. 2007). Interestingly, a recent subliminal face processing task with 9- to 12-year-olds with high levels of behavioral inhibition (Auday et al. 2018) found hyper-activation centered on the cerebellum. While this region has traditionally been viewed as a motor region, recent work has implicated cerebellar activity in triggering or maintaining the threat processing circuitry.

Interestingly, when adolescents diagnosed with generalized anxiety disorder performed the identical fMRI task (i.e.,

rating levels of internal fear or passive viewing emotional faces), they also exhibited amygdalar hyperactivation only when rating their fearful feelings (McClure et al. 2007). When presented with angry or fearful faces, adolescents diagnosed with generalized anxiety disorder showed greater amygdala activation (Thomas et al. 2001), even when the faces were presented subliminally (Monk et al. 2008). The magnitude of amygdala activation was also positively correlated with anxiety severity (Monk et al. 2008; Thomas et al. 2001). The broader clinical imaging literature in adults has also documented that a hyper-reactive amygdala response to emotionally-salient stimuli, especially if negative in valence, is a prominent neural substrate for anxiety disorders (e.g., Stein et al. 2002). Taken together, these reviewed neuroimaging findings highlight the role of the hyper-reactive amygdala as a shared neural foundation between behavioral inhibition and clinical anxiety. For individuals with early behavioral inhibition, the atypical amygdala function may help sustain their early temperamental risks over time and contribute to the later emergence of anxiety.

In addition to the amygdala, a recent series of studies suggests that behavioral inhibition may also be associated with neural regions that are traditionally implicated in reward processing, such as the striatum (Caouette and Guyer 2014). Guyer and colleagues explored reward-related processing in adolecents with behavioral inhibition. In a stratified incentive task, they found that while adolescents with or without a history of behavioral inhibition showed comparable behavioral performance, inhibited adolescents exhibited greater striatal activation in response to incentives than their non-inhibited peers (Guyer et al. 2006, 2013). In another study using a similar paradigm (Bar-Haim et al. 2009), adolescents with early behavioral inhibition displayed heightened striatal activation than their non-inhibited counterparts when they believed that the reward outcome would be contingent upon their performance. The two groups did not differ in the non-contingent conditions. When adolescents were given immediate negative feedback for their behavioral performance, greater responses in the striatal regions were again observed in inhibited versus non-inhibited adolescents (Helfinstein et al. 2011). Finally, the incentive-induced striatal hypersensitivity was replicated in a group of 10-year-old children with early behavioral inhibition in comparison to their non-inhibited peers. Behaviorally inhibited children's striatal activation was further related with their social anxiety symptoms, both at age 10 and age 13 (Lahat et al. 2018).

Collectively, these findings suggest that the striatal hyperresponsivity reliably manifests among behaviorally inhibited individuals of different ages. This reward-related hypersensitivtity may reflect their worry in anticipating uncertain outcomes, excessive motivation to avoid losses, or concern over performance when the stakes increase (Guyer et al. 2013). These processes might further serve as a potential vulnerability for developing anxiety. In the clinical literature, social anxiety is associated with dysfunctions in the striatal dopaminergic system, with similar patterns of heightened striatal response to incentives observed in adolescents with social anxiety (Guyer et al. 2012). This atypical striatal function, therefore, may constitute an additional shared neural correlate between behavioral inhibition and anxiety.

Attentional Bias to Threat

The shared neural foundations that may tether behavioral inhibition and anxiety must be assessed within the context of additional factors that shape its expression. For instance, researchers have also investigated the cognitive correlates of behavioral inhibition and its association with anxiety. The notion that perturbed cognition plays a central role in the development of mental health problems originates from classic cognitive theories of psychopathology, which postulate that an individual's cognitive processing biases may serve as an important causal mechanism for disorder (Clark and Beck 1999). "Cognition" may encompass hierarchical levels of multiple information processing stages, from the early, immediate attentional processing (i.e., which aspects of the environment the individual attends to), to the later stage of interpreting attended-to events, and eventually, the consolidation of events into memory.

With respect to anxiety, much of the work has focused on early attentional processing. Specifically, attention biases to threat are evident in clinically and sub-clinically anxious youth and adults, relative to healthy controls (Bar-Haim et al. 2007). Importantly, much of this literature has been predicated on the notion that biases to threat play a causal role in developing anxiety. This argument was initially supported by longitudinal evidence from adults, which found that adults' threat-related bias predicted their later anxious symptoms in response to a stressful event (MacLeod and Hagan 1992). Evidence for causality also came from studies that experimentally manipulated individuals' attention bias. For instance, adult participants were systematically trained to attend to threat, with subsequent increases in anxiety, or away from threat, which diminished anxiety (MacLeod et al. 2002). The enthusiasm generated by early findings were such that interventions have been developed and deployed, although there is insufficient systematic evidence for the efficacy, mechanisms, and longevity of initial shifts in functioning (Mogg et al. 2017).

Researchers have also studied attention bias profiles in behaviorally inhibited individuals and observed similar patterns of heightened attention bias to threat. The initial study of attention bias in behavioral inhibition (Pérez-Edgar et al. 2010a) found that adolescents with a history of early childhood behavioral inhibition, without any anxiety diagnosis, showed elevated attention bias to threat

relative to their non-inhibited peers. Threat-related attention bias also appeared to moderate the relation between behavioral inhibition and later anxious behaviors: early behavioral inhibition predicted increased social withdrawal in adolescence, but only for adolescents who also showed greater attention bias to threat. Interestingly, this is the only study that observed heightened threat bias in behaviorally inhibited youth. However, the moderation pattern has been replicated in other behaviorally inhibited samples. Behavioral inhibition in toddlerhood prospectively predicted high levels of social withdrawal at 5-year-old, but only for children who displayed an attention bias to threat at age 5 (Pérez-Edgar et al. 2011). Another longitudinal study (Pérez-Edgar et al. 2010b) found that low sustained attention to targets and elevated attentional vigilance toward distractors in 9-month-old infants was associated with greater inhibited behaviors during toddlerhood and middle childhood. Further, the association between childhood behavioral inhibition and social discomfort during adolescence was significant only for individuals with heightened vigilance as infants. These observed moderation effects suggest that for children and adolescents with a history of behavioral inhibition, the presence of attention bias to threat might further pull them toward a developmental pathway characterized by elevated anxiety symptoms.

As with the much of the behavioral inhibition-anxiety literature, recent studies have focused on documenting neural parallels to observed attention patterns. For example, when completing a commonly used attention bias paradigm (i.e., the dot-probe task), anxious adolescents typically display aberrant activation patterns within the fronto-limbic network in comparison with healthy controls, including greater dlPFC activation (Telzer et al. 2008) and attenuated amygdala deactivation (Price et al. 2014). The effect appears to be most robust when the participant must work to shift attention away from threat. To date, two studies have examined the same task in healthy youth characterized for behavioral inhibition (Fu et al. 2017) and young adults with a history of behavioral inhibition (Hardee et al. 2013). In Fu et al., 9- to 12-year-old children with high behavioral inhibition displayed greater activation in dlPFC than their non-inhibited peers when they had to shift attention away from threat. In Hardee et al., young adults with a history of stable early childhood behavioral inhibition showed stronger negative fronto-amygdala connectivity than individuals without behavioral inhibition in response to angry versus neutral faces. In each case, the pattern observed in the behavioral inhibition sample was associated with levels of anxiety, suggesting that these mechanisms may reflect how at risk individuals do (or do not) respond in the face of threat.

Parenting

The immediate environment of children and adolescents typically includes parenting behaviors, inter-parental relations, parental psychopathology, peer relations, and teacher-student relationships. Due to space limitations, this article focuses on the strongest single force shaping their experienced environment, parenting. An extensive literature has documented the critical role of parenting in influencing children and adolescents' socioemotional development (McLeod et al. 2007). Consistent with a developmental perspective, this literature highlights the interplay between parenting and other factors, such as early child temperament (Kiff et al. 2011), to shape functioning over time. As a complex, multi-faceted behavior, parenting has been conceptualized in different ways. The current review focuses on two types of parenting behaviors that have been commonly studied in the context of behavioral inhibition, overprotection and intrusiveness. Within this literature, two lines of research have emerged. One focuses on the interactions between behavioral inhibition and parenting in predicting anxiety, emphasizing how one construct moderates the effects of the other on adjustment outcomes. A different model of research emphasizes a bidirectional relation between behavioral inhibition and parenting. This line of studies often capitalizes on longitudinal data, highlights the potential reciprocal transactions between temperament and parenting, and implies mediational pathways towards outcomes.

Interactions Between Behavioral Inhibition and Parenting

Overprotective parenting, sometimes labeled as oversolicitous parenting, is conceptualized as parental restrictions on their children's exploration in new environments. Oversolicitous parenting often steps in to provide excessive comfort to the child, particularly when not warranted (Ungar 2009). Inhibited toddlers and preschoolers of overprotective parents tend to show greater stability of behavirol inhibition, and a greater likelihood in showing anxious behaviors, than their equally-inhibited peers with less protective parents (Hastings et al. 2008; Rubin et al. 2002). Similar patterns were observed in other parenting behaviors marked by "overly" sensitive or high-warmth parenting. For instance, Mount et al. (2010) found that high levels of maternal sensitivity was correlated with more concurrent anxiety symptoms for inhibited toddlers, relative to their non-inhibited peers. Park et al. (1997) found that for highly negative reactive infants only, more "supportive" parenting (i.e., higher sensitivity and lower intrusiveness) during the second and third years of life was correlated with increased inhibited and anxious behaviors at age 3. Overall, overprotection or oversensitivity may have prevented inhibited children from learning independent coping skills when facing challenges from the

environment, and therefore maintained or exacerbated their inhibited and anxious responses to novelty and uncertainty over time.

Another parenting behavior that has been associated with behavioral inhibition is intrusiveness. Intrusive parenting is defined as parental control over children that commands or constrains children's behaviors (Wood 2006), and has sometimes been labelled as overcontrol or low autonomy granting (van der Bruggen et al. 2008). In the context of behavioral inhibition, intrusive parenting occurs when parents push their children to interact with an unfamiliar situation in a forceful way. Similar to the negative effect of overprotection, behaviorally inhibited children of intrusive parents show higher stability of inhibition and increased risks for later anxiety. For instance, toddlers' inhibited behaviors at age 2 significantly predicted their social reticence at age 4, but only when their mothers showed more intrusive behaviors at age 2 (Rubin et al. 2002). Similar effects have been found in other parenting behaviors related to intrusiveness, such as derision and criticism. For example, inhibited toddlers of highly derisive mothers showed sustained inhibition and social reticence, compared to their peers with non-derisive mothers (Rubin et al. 2002).

The detrimental effect of intrusiveness and related parenting behaviors may be due to the fact that it overwhelms inhibited children's coping capacities when they are already stressed by the novel circumstances, and thus enhances their feelings of being out of control (Chorpita and Barlow 1998). Intrusiveness may also induce in children heightened negative emotional arousal, which may further disrupt their ability to self-regulate (Nachmias et al. 1996). This line of studies suggests that the effects of early behavioral inhibition may be potentiated by variations in parenting behaviors, which color the emotional tone of the child's immediate environment. Interestingly, these two types of parenting behaviors, overprotection and intrusiveness, appear to be quite different from each other. Yet, they show similar effects, perhaps rooted in the fact that children are prevented from effectively facing, and adapting to, novelty across contexts.

Bidirectional Relations Between Behavioral Inhibition and Parenting

In addition to the moderating effects of parenting on the link between behavioral inhibition and socioemotional outcomes, bidirectional relations are also obsesrved between behavioral inhibition and parenting. A central tenet of the developmental psychopathology perspective is that while individuals are influenced by the environment, they also play an active role in shaping their environments (Sroufe and Rutter 1984). These relations are evident in the first months of life, but can take on a larger role as children take on greater autonomy to choose and navigate their environments (Davies and Cicchetti 2004). Studying these bidirectional relations is critical to better understanding the mechanisms underlying the developmental trajectories related to behavioral inhibition, potentially pointing to mediational pathways from behavioral inhibition to anxiety. Examining and inferring directionalities is also more challenging, as it usually requires cross-lagged data collected across multiple time points and more stringent statistical control. Hence, while studies have been accumulating along this line of research, the findings remain preliminary and mixed.

In examining the impact of parenting on the child, longitudinal data report that overprotective parenting at age 2 predicted later increases in toddlers' fearful inhibition at age 4, above and beyond the stability of children's inhibited behaviors over time (Rubin et al. 2002). Similar patterns were observed in studies of preschoolers, where protective parenting predicted children's inhibited and fearful behaviors a year later, even when accounting for the stability of children's inhibition (Edwards et al. 2010). In another study (Rubin et al. 1999), however, parents' self-reported overprotective behaviors at age 2 failed to predict parent-reported behavioral inhibition at age 4. Yet, another study with toddlers found that over and above the effect of early negative reactivity during infancy, certain "negative" parenting behaviors observed at 27- and 33-months, including lower sensitivity, less positive affect and greater intrusiveness, predicted decreased inhibited behaviours in children when they were 36- to 37-months-old (Park et al. 1997). These longitudinal patterns converge with findings from the interaction studies reviewed above. Overall, parental overprotection tends to worsen the negative impact of behavioral inhibition on mental health outcomes, either by conditioning the effects of behavioral inhibition on later anxiety or directly leading to increased levels of behavioral inhibition, which in turn confer greater risks for anxiety.

In older children, inconsistent parental discipline at age 9 predicted increases in children's fearful inhibition a year later, above and beyond the stability of inhibition (Lengua and Kovacs 2005). However, in another study conducted on the same cohort, higher initial levels of inconsistent discipline at age 9 predicted modest decreases in inhibition 2 years later (Lengua 2006). It is interesting that opposite patterns were generated from the same longitudinal dataset, when different developmental periods were examined. As interpreted by the author, it is possible that as youth are transitioning into adolescence, that is from 9- to 11-year-olds, they might perceive highly consistent parenting as overcontrol and inconsistent parenting as more "autonomy granting". This perceived autonomy may result in decreased inhibition. This study also found that higher initial parental rejection at age 9 predicted modest increases in fearful

inhibition, and in turn internalizing problems, at age 11 (Lengua 2006).

In tandem, there is evidence supporting the impact of behavioral inhibition on parenting, demonstrating the evocative effects of child temperament in eliciting specific parenting behaviors. Much of this work has focused on the influence of early childhood behavioral inhibition on protective parenting. Specifically, it is conceptualized that inhibited children, compared with their non-inhibited peers, may be more likely to elicit overprotection from parents, especially when they show fearful responses to novel and uncertain situations. Longitudinal data suggest that parental report of toddler's inhibition predicted parents' future overprotection and disencouragement of independence, when accounting for the stability of parenting behaviors (Rubin et al. 1999; Hastings and Rubin 1999). Overprotection may in turn reinforce toddlers' inhibited behaviors and increase the likelihood of developing anxiety, playing a mediating role between early behavioral inhibition and anxious behaviors a year later (Kiel and Buss 2009). Similarly, in older children higher levels of fearful inhibition at age 9 predicted increased parental acceptance a year later, and modest decreases in parental rejection over the next 2 years, even while controlling for stability of parenting (Lengua and Kovacs 2005).

Interactional (moderational) and bidirectional (potentially mediational) processes are likely to coexist in shaping the pathway from early behavioral inhibition to later anxiety. For instance, parental overprotection may both moderate the effects of behavioral inhibition on anxiety and, at the same time, lead to increased levels of behavioral inhibition at a later time, above and beyond the stability of behavioral inhibition. Park et al. (1997), for instance, reported the interactional relation between parenting and negative reactivity during infancy in relation to inhibited behaviors in toddlerhood. That is, more supportive parenting behaviors were associated with toddler's higher inhibition only for those with high negative reactivity during infancy. In the meantime, they also observed a directional relation from parenting during ages 2–3 to child inhibited behaviors at age 3, over and above the stability of early behavioral inhibition.

A Proposed Conceptual Model

The above sections have reviewed studies examining the relations between behavioral inhibition and other factors from different systems, and how these relations shape the the links between behavioral inhibition and anxiety. Bringing these studies together illustrates the integrative approach of developmental psychopathology. Based on the extant empirical evidence, as well as theoretical perspectives in this area, this review proposes a conceptual developmental model to illustrate the potential pathways from behavioral inhibition to later outcomes (Fig. 1). This model aims to provide an abridged summary of the literature and proposals for the multi-determined developmental mechanisms of the behavioral inhibition-anxiety link. It also highlights directions that warrant future research.

First, the link between behavioral inhibition and anxiety may be fueled by their shared neurobiological foundations, which are centered on, and related to, hyper-reactive amygdalar function. Specific patterns of activity and connectivity within these neural correlates might also play a moderating role. For example, as described above, extreme patterns of neural dysfunction might strengthen the stability of behavioral inhibition and its association with later anxiety. The behavioral relation between behavioral inhibition and anxiety is also moderated by individual differences in the cognitive domain, such as cognitive processing bias. As shown in the reviewed literature, substantial evidence has been reported that inhibited individuals who are also biased toward threat are more likely to develop anxiety. These moderation patterns suggest that when more than one risk factor are coupled together, they generate a "richer" context of risk and boost the probability for developing maladaptative outcomes. For example, the relation between behavioral inhibition and anxiety symptoms in 9- to 12-year-olds was strongest for individuals who also showed an attention bias towards threat and right frontal EEG asymmetry. On the other hand, inhibited children with a pattern of left frontal EEG asymmetry and avoidance of threat showed lower levels of anxiety (Vallorani et al. under review).

To date, less work has investigated if there exist any bidirectional relations between behavioral inhibition and cognitive bias. As suggested by the behavioral inhibition literature, early vigilance towards novel or potentially threatening stimuli during infancy may grow out of a hyper-sensitive amygdala response. As children develop, the early vigilance patterns may initiate a cascade of biasing effects on later-emerging, higher-order cognitive processes, such as poor attentional control, negative interpretation of events and subsequent memory consolidation. These processes may influence each other through a feedback loop and eventually form a maladaptive cognitive repertoire, which reciprocally maintains and reinforces inhibited behaviors over time (Crick and Dodge 1994). In Fig. 1, this potentially bidirectional path between behavioral inhibition and cognitive processes is presented in dashed lines, indicating the lack of evidence in the current literature and need for future research.

Further, these individual processes constantly influence, and are influenced by, the environment that individuals are embedded in. Compared with the cognitive processes, more studies have explored the directional relations between behavioral inhibition and environmental factors such as parenting. As reviewed above, both interactional and

bidirectional relations are observed between behavioral inhibition and parenting behaviors, which in turn predict anxiety outcomes. Parenting may serve as both a moderator and a mediator in tethering behavioral inhibition to later anxiety.

There may also exist interrelations between these additional risk factors across different systems. For instance, children who are constantly exposed to negative parenting (e.g., verbal abuse) might become oversensitive, or highly biased, in detecting angry/threatening cues (Pollack et al. 2000). Exposure to high inter-parental conflicts is also found to be associated with hyper limbic activation in response to angry voices in the developing brain (Graham et al. 2013). These multiple risk factors may reinforce each other, and further moderate or mediate the link between behavioral inhibition and anxiety. However, little work has directly explored the interplays between multiple risk factors in the context of behavioural inhibition-anxiety relation (dashed lines between endogenous and exogenous factors in Fig. 1). The extant studies typically focus on a limited number of variables and examine relatively narrow slices of the wholistic developmental picture. The complexity in the behavioral inhibition-to-anxiety trajectory, as speculated in the proposed model, highlights the need to simultaneously examine multiple relations between multiple processes. Future longitudinal studies with three or more time points, large sample size, and measures of multiple constructs will be needed to build statistical models that are able to tap into the multiple moderation and mediation paths among constructs of interest. The complexity of such designs will need collaborations that span multiple labs in order to harness the requested resources and expertise. In this way, these studies can be modeled on (although not necessarily match) current larger scale projects such as the Environmental Influences on Child Health Outcomes (ECHO) study and the Adolescent Brain Cognitive Development (ABCD) study. Only in doing so will researchers be able to delineate the intricate relations within the larger picture, which emerge and recede as the systems of interest move through developmental windows and environments, with evolving goals and challenges.

Translational Implications and Future Directions

The above sections have reviewed extant developmental psychopathology evidence for the multiple potential mechanisms underlying the behavioral inhibition-anxiety link. In addition to adding to the understanding of the etiology of children and adolescents' anxiety, these findings also point to several directions for developing refined, and more targeted, prevention and intervention tools for anxiety in children and adolescents. Developing such tools for healthy yet at-risk populations such as individuals with behavioral inhibition, and implementing these tools in the target population as early as possible, is critical for effectively preventing the incidence of clinically significant disorder. Importantly, the lessons from the developmental psychopathology literature illustrate that the prevention/intervention approaches cannot be static or rigid, as this does not reflect the dynamic nature of the processes of interest.

As discussed earlier, for individuals with a history of early behavioral inhibition, their attention bias toward threat might significantly strengthen the links between behavioral inhibition and later anxiety. Accordingly, training inhibited individuals to shift their attention away from threat might be an effective way to diminish their anxiety symptoms and lessen risk for clinical anxiety disorder. In the clinical literature, attention training has been implemented through a computerized attention bias modification (ABM) task, with positive effects reported in alimorating levels of anxiety (Linetzky et al. 2015). In the context of temperamental risk, a recent study examined the use of ABM in a group of healthy yet behaviorally inhibited youth ages 9–12 (Liu et al. 2018). The authors observed a positive effect of ABM in reducing parent-reported anxiety symptoms as well as accompanying changes in frontolimbic activity. Interestingly, these changes were not accompanied by changes in reaction-time based measures of attention bias. Compared with other intervention approaches for anxiety, computer-based attention training programs are easy for children and adolescents to understand and complete. They are also low cost and could be easily conducted and disseminated in non-clinical settings. Despite this promise, recent work has raised concerns regarding the strength of the initial published effects (Mogg et al. 2017). In particular, the overall effect size for attention bias based on the most commonly used tasks may be low and variable, likely due to its poor psychometric properties (Rodebaugh et al. 2016). The smaller, recently emerging literature relying on additional markers of attention, such as eye-tracking, ERPs, and fMRI, seem to be more promising (e.g., Liu et al. 2018; Sanchez et al. 2013). While future studies are warranted to fully understand the underlying mechanisms and optimize the design and implementation of ABM, this approach may prove a promising and economical prevention/intervention tool for anxiety-prone children and adolescents.

Given the observed relations between behavioral inhibition and specific parenting behaviors, interventions that target parents may be another useful way in protecting their behaviorally inhibited children from anxiety. Indeed, many interventions for young children bypass the child and instead focus on the parents (Rapee et al. 2005). As reviewed earlier, researchers have found that both parental overprotection and intrusiveness tend to exacerbate the negative impact of behavioral inhibition, either by conditioning the effects of behavioral inhibition on later anxiety (interactional effect)

or directly leading to increased levels of behavioral inhibition (directional effect). Buss and Kiel (2013) suggest that there may exist a curvilinear relation between parenting and children's inhibited and anxious behaviors. Specifically, both protective and intrusive parenting can be mapped onto a continuum of the parent's "encouragement to approach/engage with novelty", with intrusiveness residing on one extreme and overprotectiveness on the other. Both ends are associated with sustained inhibition and increased risk for anxiety. Therefore, it is important for parents of inhibited children to balance their protectiveness and warmth with firm limit setting when their children are facing novelty and uncertainty. Interventions that promote parenting strategies of gently encouraging inhibited children to engage with novelty at a slow pace, modeling effective coping skills, and providing support when children are overwhelmed, may prove especially helpful. This "gentle encouragement" strategy is likely associated with optimal outcomes for behaviorally inhibited youth.

Along this line, Rapee, Bayer, and colleagues (Rapee 2013; Rapee et al. 2005, 2010) conducted a series of studies (the "Cool Little Kids" program) exploring the effect of parental intervention in diminishing behaviorally inhibited children's withdrawal and anxious behaviors. Their intervention strategies centered on teaching parents of inhibited preschoolers to reduce their protectiveness and supportiveness when their children avoid novel circumstances, and to systematically model and promote active approach skills when facing unfamiliar situations. Overall, they found positive effects for the active parenting intervention at multiple points of follow-up, indicated by lower incidence rates of anxiety and other internalizing disorders through middle adolescence, in comparison with the control, no intervention, group. These effects were further moderated by child sex, parents' motivation in engaging in the intervention, and parental history of psychopathology. These studies provide important evidence for parenting intervention as a tool in protecting children with early behavioral inhibition from anxiety.

Of note, the extant parenting interventions focused on reducing overprotective behaviors in parents of preschool children. Little is known if the observed effects would generalize to youth at older ages. As reviewed in the sections above, similar parenting behaviors might have different impacts on youth of different ages, such that consistent parenting might be perceived by adolescents as more intrusive and less autonomy granting and therefore have a negative impact on their adjustment (Lengua 2006). Consideration of age appropriate processes is therefore critical in developing and implementing parenting intervention strategies in future studies.

In addition to interventions targeting the potential moderators or mediators in the developmental model, another line of intervention directly focuses on modifying the manifestations, or "outcomes", of behavioral inhibition. As inhibited children grow up, they typically show social withdrawal and poor social skills, tend to have fewer friends, and experience more social rejection (Burgess et al. 2006; Pedersen et al. 2007). Thus, prevention and intervention efforts focusing on improving their social skills and social competence may help them overcome these difficulties, and therefore ameliorate risks for developing clinically significant social anxiety. Two intervention studies (the "Social Skills Facilitated Play" program) taught inhibited preschoolers core social skills to initiate and maintain social interactions (Coplan et al. 2010; Li et al. 2016). At 3- and 6-month follow-ups, children who received active intervention showed lower levels of social wariness and greater social competence and prosocial behaviors, compared with their inhibited peers receiving no intervention. While the current studies focused on preschool children, this strategy may also be helpful for adolescents who are experiencing anxiety problems and social difficulties. Adolescence marks a critical period of meeting social challenges such as developing peer relations and romantic relationships (Scherf et al. 2012). Intervention strategies directly improving these skills may be particularly useful. Future studies that investigate the effects of social skill training in adolescents with inhibited and anxious behaviors will provide important evidence for the implementation of this approach in clinical and non-clinical settings.

Given the multi-faceted nature of the processes that link behavioral inhibition to anxiety, using a combination of multiple strategies that simultaneously target multiple constructs of interest might further enhance the effects of intervention. Recent work has conducted intervention programs on behaviorally inhibited preschoolers using combined multi-session parenting intervention and child social skill training and observed positive effects (Chronis-Tuscano et al. 2015; Lau et al. 2017). For instance, at 6-month follow-up, preschoolers in the combined intervention group showed significantly fewer clinician-rated and maternal reported anxiety symptoms compared with a waitlist control group. At 12-month follow up, the combined intervention group showed a greater reduction in clinician-rated, but not maternal reported, anxiety symptoms in comparison with a parenting intervention only group (Lau et al. 2017). These results provide evidence for the feasibility and efficacy of using a combined intervention approach for the at-risk youth population. Future studies with larger scale and longer follow up are needed to examine the effects of different combinations of intervention strategies, including parent- (and teacher-) focused intervention, and youth-focused cognitive and social intervention.

Finally, the neural correlates of behavioral inhibition reviewed earlier may serve as biomarkers that predict the impact of individual prevention and intervention strategies. In the current literature, this has been primarily examined

with fMRI measures. In an fMRI study examining the effect of ABM in behaviorally inhibited children (Liu et al. 2018), inhibited children who displayed higher amygdala/insula activation or lower vlPFC activation at baseline benefited more (i.e., showed greater anxiety reduction) from attention training. This pattern echoes previous findings in clinically anxious adult samples indicating that their baseline fronto-limbic functioning predicts anxiety reduction following various treatments, including ABM (Britton et al. 2015), cognitive-behavioral therapy (Klumpp et al. 2013), and medication (Faria et al. 2012). Identifying baseline bio-markers could help identify which individuals will be more likely to respond to a prevention/intervention strategy. This targeted information may help increase, from the outset, the efficacy of treatments for anxiety-prone children and adolescents. Nonetheless, obtaining fMRI measures for identification would be costly and difficult, especailly for young children. Future studies are warranted to examine and identify other candidate bio-markers that are more accessible and youth-friendly (e.g., psychophysiological measures) to researchers and clinicians.

Conclusion

Anxiety problems emerge early during development and exacerbate during adolescence. Taking a dynamic, developmental approach to examine the mechanisms underlying the broader spectrum of socioemotional functions, rather than a "snapshot" like, symptom-based approach of diagnostic classification, is important for understanding the etiology of the disorder. It is also needed for creating targeted early prevention/intervention tools prior to the development of clinically significant symdromes, which most typically emerge during adolescence. This article reviewed developmental psychopathology research focusing on behavioral inhibition as a prominent, early etiological factor for children and adolescents' anxiety. As propsed in the developmental model, early behavioral inhibition is associated with later anxiety through multiple pathways that span multiple systems. First, this association may be fueled by shared neural foudations underlying these two constructs, which is centered on a hyperreactive amygdala. Behaviorally inhibited children and adolescents may also elicit specific responses from their environment, e.g., overprotective parenting and social rejection, which might in turn reinforce their inhibited behaviors and strengthen the behavioral inhibition-anxiety association. This association is also moderated by individual differences in other domains such as congnive processing biases. However, it is unclear if there exists bidirectional relations between behavioral inhibition and negatively biased cognitive processing, and if and how the interaction between cognitive and environmental factors contributes to the behavioral inhibition-anxiety association. Future studies that employ a large scale, intensive longitudinal approach with measures of multiple constructs and processes are warranted.

Generating knowledge regarding the early etiology and pathophysiology of anxiety disorder will accelerate researchers' and health practitioners' ability to support adaptive development for children and adolescents at individual and systemic risks for anxiety. In particular, early prevention/intervention strategies that target the specific moderators and mediators as proposed in the developmental model will break the chains linking behavioral inhibition to later negative outcomes. This is particularly critical for at-risk children who are transitioning into adolescence, which is a high-risk period for the incidence of clinical anxiety disorders. It is therefore important to dentify risk markers as early as possible. Given that behavioral inhibition can be identified as early as toddlerhood, the time window between toddlerhood and early adolescence may be critical for implementing targeted preventions to prevent clinical disorders. Future prevention studies focusing on different stages within this time window will inform the prevention practices for high-risk children and adolescents in both the clinical and community contexts. Finally, for children and adolescents who already developed clinical anxiety, taking the developmental psychopathology perspective will also help identify the primary causal factors that lead up to the full-scale syndromes, predict the trajectories of illness, and importantly, inform more targed treatment selections.

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Compliance with Ethical Standards

Conflict of Interest The authors report no conflict of interest.

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