Temperamental risk for anxiety: emerging work on the infant brain and later neurocognitive development

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Abstract

Behavioral inhibition (BI), an infant temperament characterized by distress to novelty, is amongst the strongest early risk markers for future anxiety. In this review, we highlight three ways that recent research elucidates key details about the pathophysiology of anxiety in individuals with BI. First, atypical amygdala connectivity during infancy may be related to BI. Second, developmental shifts in cognitive control may portend risk for anxiety for children with BI. Lastly, distinct cognitive control processes moderate the BI-anxiety relation in different ways. Studying the intersection of these three streams of work may inform prevention or intervention work.

Behavioral inhibition (BI), an infant temperament characterized by distress to novelty, is amongst the strongest early risk markers for anxiety. Relative to other temperaments, children with BI face sixfold increase risk for social anxiety [1]. While not all individuals with a history of behavioral inhibition experience social anxiety, many have difficulty navigating social situations. Compared to their peers, children with BI display hyper-sensitivity to novel social situations, experience more social rejection from peers, and experience loneliness and social isolation into adulthood [2••,3]. Despite considerable interest in the origins of BI and pathways to anxiety, the neural mechanisms remain elusive.

Decades of longitudinal research have linked both BI and anxiety to functioning in a distributed network encompassing the amygdala and prefrontal cortex (PFC). Adults and adolescents exhibit atypical amygdala activation and amygdala-PFC connectivity [4–6]. These and other findings [7–10] suggest that salience detection and the regulation of goal-directed behaviors through cognitive control impact risk trajectories for individuals with

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BI. Nevertheless, precise details about the neurodevelopmental pathways to anxiety remain underspecified. In this review, we highlight three ways in which recent research reveals some of these details about the pathophysiology of anxiety in individuals with a history of BI.

Identifying neural markers of temperamental risk for anxiety in infancy

Growing research finds that children with BI show perturbed attentional processing [11–15]. Yet, relatively little research identifies neural correlates of BI before middle childhood (although see Ref. [16]). A full understanding of anxiety pathophysiology in individuals with a history of BI might arise through neuroimaging studies before the onset of BI. Acquiring such data beginning in infancy has been a focus of recent research.

Temperamental differences in distress to novelty manifest as early as 4 months of age and are associated with developing BI in toddlerhood [17]. Both BI and 4-month distress to novelty are traditionally assessed in the lab by presenting novel stimuli to infants. However, unlike BI which is quantified by avoidance behavior in toddlerhood (ages 1–3), 4-month reactivity to novelty is quantified as heightened motor arousal and affective response, given limitations of 4-month-olds' behavioral repertoire. Recent work shows that at four months of age, elevated novelty-evoked distress relates to greater amygdala-cingulate resting state functional connectivity [18••; rsfc; See Figure 1]. A similar pattern of stronger neonatal amygdala-cingulate rsfc was associated with high fear and cognitive development (as assessed using the Bayley Scales of Infant and Toddler Development's cognitive scale[5] [19]) at 6 months and with greater generalized anxiety symptoms at age 2 [20]. However, neonatal imaging studies also find that amygdala connectivity with the insula [21], ventral striatum [22], and medial PFC [20] relates to maternal report of fear [21,22] and internalizing symptoms [20]. Still other studies link stronger amygdala-precuneus/cuneus connectivity changes between ages 1 and 2 to greater anxiety at age 4 [23]. Observed 4-month distress to novelty as well as maternal report of fearful temperament and internalizing symptoms all relate to BI, but the strength of each association is modest (typically $r \sim 0.3$). Thus, there are not one-to-one mappings amongst these measures. Additional work mapping relations among each measure and comparing brain-behavior associations using maternal report and observational assessments of temperament is needed.

Additionally, evaluating the association between rsfc in infancy and BI in toddlerhood will be critical. To date, only one study has examined this longitudinal association. Using whole-brain connectivity mapping, Sylvester *et al.* found that decreased connectivity between the ventral attention and default mode network was associated with greater maternal report of BI on the Infant-Toddler Social and Emotional Assessment at age 2 [24]. Future work should prioritize longitudinal studies extending this work that include behavioral assessments of temperament. Reliably tracking these associations will require acquiring large (n 200) longitudinal datasets [25] with both rigorous behavioral assessments and parent report measures.

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[5]The Cognitive scale of the Bayley indexes several key behaviors including sensorimotor development, an infant's capacity for object manipulation, memory, and concept formation.

These initial studies link temperament to brain circuitry that supports attention to threat (e.g. amygdala-PFC connectivity, ventral attention network connectivity). However, important developmental questions remain about the origins of these relations. If, as the work suggests, meaningful individual differences in brain function manifest at birth, this could implicate prenatal or genetic factors in connectivity. Indeed, several new studies of maternal mood and stress during pregnancy find relations with brain development and temperament [26–30]. However, these relations could involve multiple factors, including genetics, epigenetic factors, and stress hormones. Data obtained during pregnancy could further delineate the factors that shape newborn functional connectivity.

One valuable extension of this work would be to directly evaluate how the brain processes novelty using task-based imaging (e.g. functional magnetic resonance imaging [fMRI] and/or electroencephalography [EEG]). For example, the auditory oddball can be conducted both while infants are sleeping in the scanner and while collecting awake EEG. Recent task-based fMRI work links high maternal anxiety to greater neonatal brain responses to novelty–specifically, in the insula, ventrolateral prefrontal cortex and anterior cingulate [31]. Still other studies have used awake task-based infant fMRI to link prefrontal cortex function to stimulus-driven attention [32]. Novel insights might arise through extensions of this work linking infant temperament to novelty detection as assessed via EEG and fMRI.

Together, extant work suggests that the neural correlates of temperament manifest at birth and may persist through the first four months of life. While this implies some early stability, more longitudinal work is needed. Stable temperamental differences in the neural correlates of novelty or threat detection may exist early, as quantified through imaging. Alternatively, measurable neural correlates may change with experiences. In the next sections, we expand on research exploring how developing cognitive control circuitry may change with time.

Understanding developmental changes in cognitive control

Broadly speaking, new studies of the infant brain have begun to suggest that temperamental distress to novelty relates to functions in brain circuitry that supports attention to threat. However, it remains unclear how developing behavioral control circuitry might impact early attentional processes. Additionally, the process by which control shapes risk remains underspecified, particularly in early childhood when control processes develop rapidly. In this section, we highlight a few key developments in these areas.

Longitudinal neuroimaging work connecting temperament, neurocognitive development, and anxiety has been limited. Nevertheless, several advancements have been made in this area using behavioral methods. For example, Troller-Renfree *et al.* [33•] examined how changes in inhibitory control (IC) on a Go/NoGo task relate to risk for anxiety. In this study, BI was assessed in toddlerhood, IC was assessed at ages 5, 7, as well as 10 using a child-friendly Go/NoGo task,[6] and social anxiety symptoms were assessed at age 12 [33•]. Signal detection theory was used to deconstruct IC into separate discrimination and response bias measures,

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[6]The Go/NoGo task (also known as the 'zoo game') is a neutral child-friendly task with no explicit incentives or post-trial feedback. Children were instructed to press a button when they saw an animal (Go trials), withholding responses for monkeys (NoGo trials).

with discrimination reflecting the participant's ability to distinguish between 'go' and 'no-go' trials, and response bias reflecting the participant's tendency to respond on any trial regardless of the stimulus type. Although IC response bias did not change from age 5 to 10, IC discrimination improved. Further, the rate of change moderated relations between BI and social anxiety. Specifically, those individuals with BI who exhibited greater age-related increases in IC discrimination exhibited greater social anxiety at age 12. This finding aligns with the notion from attentional control theory that anxiety is associated with reduced efficiency of certain types of control, including IC [34,35]. This work suggests that changes in IC may portend risk for anxiety for children with BI. Thus, mapping developmental changes in cognitive processes are essential to understanding risk trajectories.

Continued follow-up of these same youth with other behavioral tasks revealed additional insights. In addition to improvements on simple IC tasks, performance also improves with age on more complex tasks, such as those involving frequent changes in rules or context. One such task is the AX Continuous Performance Test (AX-CPT) [36,37], which presents letter pairs, with a cue and probe letter (see Figure 2). Participants make a target response when they see a particular cue-probe combination (i.e. the letters 'A' followed by 'X'). Thus, successful performance depends, in part, on the ability to detect differences in context. That is, the letter 'X' is a target stimulus only if it follows an 'A'. One can derive a behavioral measure (i.e. d' context [37]) that reflects the participant's ability to distinguish between target and nontarget trials as a function of the cue letter. Higher d' context scores indicate greater sensitivity to context. In contrast to Troller-Renfree *et al.* findings that greater age-related increases in IC discrimination (from age 5 to 10) increased anxiety risk for those with BI [33•], greater age-related increases in context sensitivity from age 13 to 15 years were instead associated with fewer anxiety symptoms among those with high BI (Valadez *et al.*, under review; see Figure 3). Low-BI youth, as well as high-BI youth with smaller age-related increases in context sensitivity, instead tended to experience worsening anxiety during this period. These findings suggest that both temperament and cognitive control predict risk. This work further highlights the importance of measuring change across the development and indicates that not all cognitive control processes relate to anxiety in the same way.

These findings emphasize the need for larger longitudinal studies of cognitive control—including neuroimaging studies that take a basic science approach to identifying the neural processes that underlie cognitive control in early childhood [e.g. see Ref. 36]. However, it is important to note that children's performance on these cognitive tasks changes rapidly over childhood often leading researchers to have to decide whether to prioritize maintaining an identical paradigm or maintaining comparable levels of performance across timepoints. These decisions can have important implications for interpretability, including the ability to establish temporal precedence of risk factors over symptom onset. See Box 1 for a summary of key considerations for longitudinal studies of temperamental risk for anxiety.

The heterogeneity of cognitive control and its role in anxiety risk

Research on different types of cognitive control is a third area of importance in the BI-anxiety link. One of the most consistent findings in the BI-anxiety literature notes cognitive

factors – specifically, cognitive control – to moderate risk for anxiety [15,38•]. However, recent work finds distinct cognitive control processes to moderate this relation in different ways [9]. Dual mechanisms of control (DMC) theory [39] differentiates proactive and reactive control. Proactive control involves early selection and maintenance of goal-relevant information before the occurrence of cognitively demanding events. On the other hand, reactive control involves 'late correction' on an as-needed basis, usually in response to conflict that arises with the occurrence of the event. Together, these temporally distinct and complementary processes influence responding to salient stimuli in goal-directed contexts; yet, they have differential relations with anxiety. For example, in a social interaction context, proactive control may be involved in selecting and maintaining a child's goal of playing a game with peers. While the child is playing the game, however, the perception of a peer's angry or threatening face may trigger reactive control processes that shift attention away from the game and onto the peer's expression, thus interfering with the child's proactive goal of playing the game [9]. The AX-CPT represents a particularly helpful paradigm for differentiating influences from proactive and reactive control. Because participants are instructed to only make a target response when they see an 'A' that is followed by an 'X,' they must use a combination of proactive control (i.e. adapting to changes in context as a function of the cue letter identity) and reactive control (i.e. responding to differences in the probe letter identity) to maximize performance.

Our most recent work examines children's behavioral and electrophysiological responses during the AX-CPT. This has shown that anxious BI youth and non-anxious BI youth differ in their deployment of cognitive control strategies. Increasingly low d' context scores may indicate increasingly limited use of a proactive strategy. In 13-year-olds with a history of BI, such low scores are associated with greater anxiety [38•]. Although the AX-CPT is thought to elicit both proactive (i.e. adapting to changes in context as a function of the cue letter identity) and reactive control processes (i.e. responding to differences in the probe letter identity), behavioral measures derived from this task are all based on accuracy and/or reaction times for responses given at the end of the trial (i.e. after the participant has already processed both the cue letter and the probe letter). Thus, behavioral measures of proactive and reactive control necessarily conflate the two control processes. This hinders attempts to disentangle each strategy's contributions to the BI-anxiety relation. In other words, based on behavioral data alone, it is difficult to conclude whether risk for anxiety depends on the level of proactive control (independent of reactive control), whether reactive control also plays a role (independent of proactive control), or whether anxiety risk depends on their interaction. Neural measures, however, are better able to separate the two control processes because they enable examination of activity during the individual cue-locked and probe-locked time windows. Thus, in our next follow-up of these youth at age 15, we administered an AX-CPT modified for simultaneous collection of EEG. Although we did not replicate the d' context moderation effect at this older time point (but see Section 'Understanding developmental changes in cognitive control' above for results of longitudinal analyses examining the change in d' context from age 13 to 15 years), using separate cue-locked and probe-locked event-related potentials, we found that BI was associated with anxiety only among youth who tended not to differentiate between cues during the earlier cue period (indicating a less proactive strategy) but instead differentiated between them during the later probe period

(indicating a more reactive strategy) [40•]. In other words, for BI youth, anxiety was elevated only among those with a particular profile consisting of low proactive control and high reactive control. Thus, the BI-anxiety relation depended on the *interaction* between proactive and reactive control processes.

Although this work highlights the roles of both proactive and reactive control, a key remaining question concerns how proactive and reactive control are instantiated in the brain. These control processes occur close together along both temporal and spatial dimensions (e.g. Ref. [41]). Thus, future research in this vein may need to use multimodal approaches capitalizing on the complementary strengths of electrophysiological and hemodynamic methods (e.g. fMRI) to better understand the neural mechanisms involved in proactive and reactive control. In addition to incorporating multimodal neuroimaging, this work would benefit from using more tightly controlled behavioral paradigms or computational modeling approaches to derive more specific behavioral measures of each control process. Ultimately, gaining a mechanistic understanding of how proactive and reactive control uniquely predict anxiety risk for youth with versus without a history of BI may inform the definition of distinguishable anxiety 'subtypes,' each emerging from distinct etiological pathways.

Conclusion

In summary, this review highlights several recent findings that have shed light on developmental pathways to anxiety. In doing so, we highlight key gaps in our knowledge about the neural origins of BI and its associated anxiety risk. We argue that these gaps indicate the need for future research in three key directions: (1) evaluating neural correlates of behavioral inhibition in infancy; (2) identifying neural markers of cognitive control and longitudinally assessed cognitive control across childhood and adolescence and (3) dissociating types of cognitive control (i.e. proactive/reactive control strategies) to illuminate pathways to anxiety. Together, increasing understanding of these three areas could inform prevention and intervention efforts targeting children at-risk for anxiety with a history of BI.

Acknowledgements

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• of special interest

•• of outstanding interest

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Box 1

Key Considerations for Longitudinal Studies of Temperament and Anxiety

- Large Ns and diverse samples to facilitate generalizability.

- Beginning prenatally to capture early factors that could impact later trajectories of brain and behavioral development.

- Include rigorous observational assessments of temperament rather than relying exclusively on parent report.

- Assessments of cognitive control beginning in childhood and obtained longitudinally are critical. Particularly tasks (like the AX-CPT) that dissociate proactive and reactive control.

- Concurrent brain (including both fMRI and EEG) and behavioral measures (e.g. parent report, cognitive assessments, temperament assessments) obtained repeatedly can provide key insight into both stability and change in brain and behavioral patterns.

- Benefits and limitations of keeping the task identical across longitudinal assessment timepoints versus maintaining comparable levels of overall performance across timepoints.

- Parent and child report of anxiety symptoms are associated with distinct patterns of behavior [42]. Thus, including assessments of anxiety from multiple reporters beginning in childhood could prove valuable.
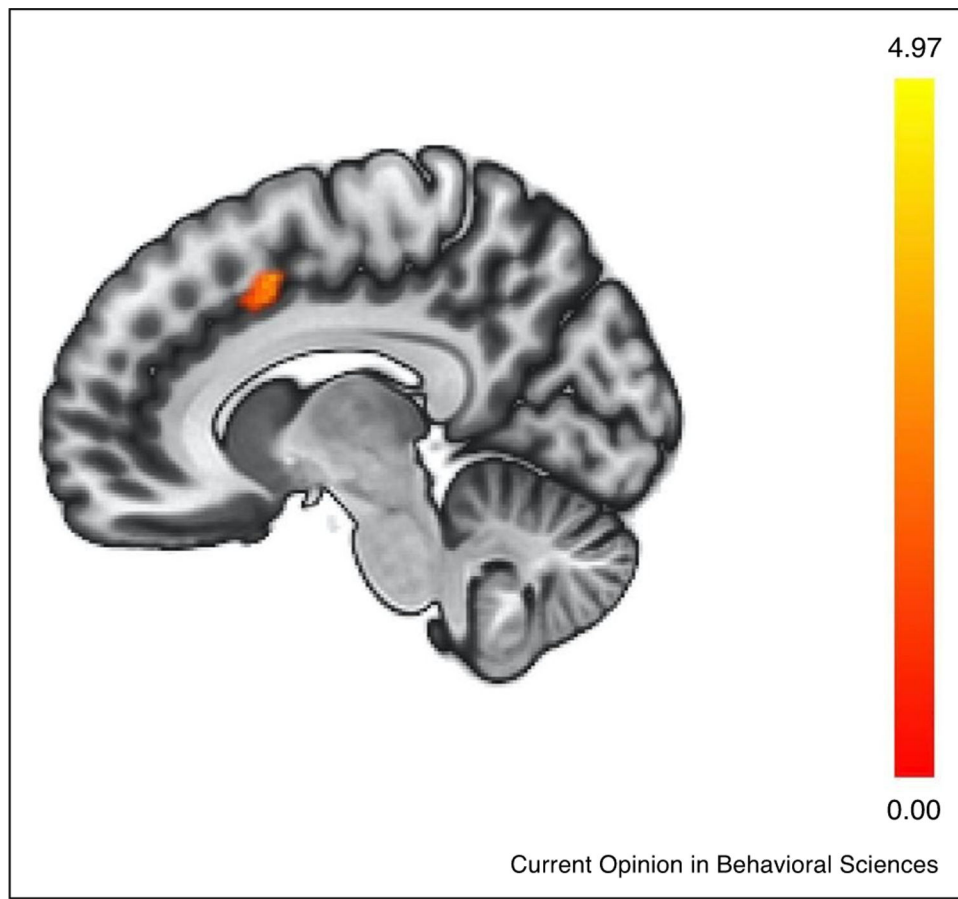
Figure 1.
Negative reactive temperament is linked to greater amygdala-cingulate connectivity at 4 months.

Note. Negative reactive temperament is characterized by high negative affect and low positive affect in the presence of novelty. Results demonstrate that amygdala-cingulate connectivity is associated with negative reactive temperament [16]. Regions highlighted include: paracingulate gyrus, anterior cingulate gyrus, and supplemental motor area. Color bar indicates t-statistic.
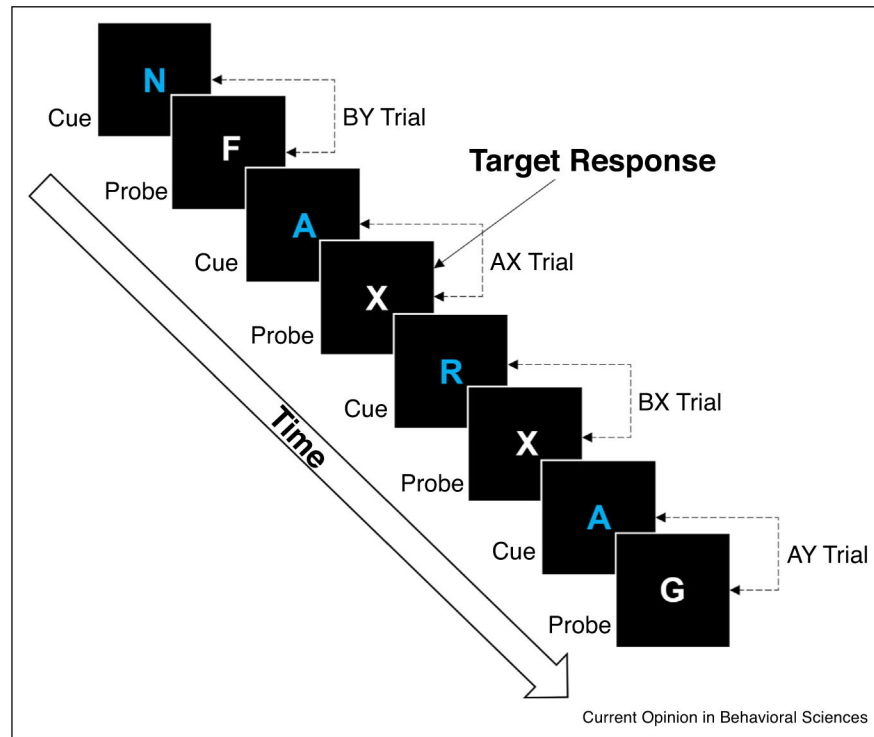
Figure 2.

AX Continuous Performance Test (AX-CPT) Schematic.

Note. Each trial of the AX-CPT consists of a cue letter followed by a probe letter. Participants press a button in response to each letter. However, when they see the letter 'A' followed by the letter 'X', they must press a different, target button. Trials are divided into four types: AX (target cue followed by target probe), AY (target cue followed by non-target probe), BX (non-target cue followed by target probe), and BY (non-target cue followed by non-target probe). D' context is a commonly used measure of proactive control derived from this task and reflects the difference in hit rate on AX trials versus the false alarm rate on BX trials; thus, it indicates the participant's ability to distinguish between target and nontarget trials as a function of the cue. Figure adapted from Troller-Renfree *et al.* [38*] *Journal of the American Academy of Child and Adolescent Psychiatry.*
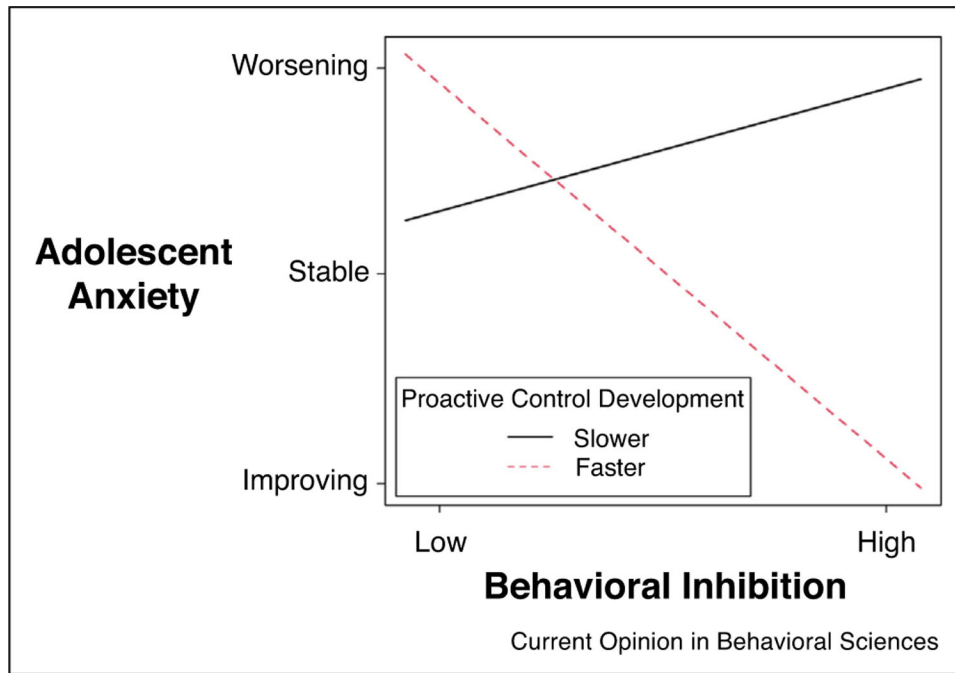
Figure 3.

Anxiety Changes Across Early Adolescence as a Function of BI and Proactive Control Development.

Note. This schematized figure illustrates real longitudinal data observed from adolescent participants from age 13 to 15 years. The x-axis reflects varying levels of behavioral inhibition. The y-axis depicts anxiety changes observed across adolescents (worsening versus improving versus stable over time). Each of the two lines indicates a different rate of proactive control development (measured as the change in d' context over time) during adolescence (slow versus fast). The schematic data presented are based on Valadez *et al.* (under review).