

# Brain Games to Reduce Anxiety in High-Risk Children

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**A**nxiety disorders are the most common class of pediatric psychiatric illness, affecting up to 30% and severely impairing up to 10% of all youth before age 18 years.<sup>1</sup> Pediatric anxiety disorders can lead to severe functional impairment and can place affected children at significantly elevated risk for anxiety, depression, and substance use disorders later in life.<sup>2</sup> Unfortunately, up to 50% of children remain symptomatic even with the best available treatment,<sup>3</sup> making anxiety disorders a major public health problem. Part of the challenge is that pediatric anxiety disorders appear to represent atypical brain development that begins in early childhood or even infancy.<sup>4</sup> Most children with anxiety disorders are identified and treated years after the onset of atypical brain development, at which point brain alterations may be irreversible. One way to overcome this challenge may be to prevent anxiety disorders from occurring in young, high-risk groups, preventing the cascade of abnormal brain development. Such an approach could have high impact, reducing the burden of pediatric anxiety disorders as well as risks associated with pediatric anxiety disorders that extend into adulthood.

In the current issue, Liu *et al.*<sup>5</sup> work from a specific neurodevelopmental model of anxiety disorders in an attempt to devise an innovative preventive strategy in high-risk children. Behavioral inhibition (BI) is an infant temperament characterized by high reactivity and distress to novel stimuli.<sup>6</sup> Longitudinal studies indicate that among behaviorally inhibited infants, those who also have an attention bias for threatening stimuli in early childhood have high levels of anxiety later in life.<sup>7</sup> With this framework in mind, Liu *et al.* propose that reducing attention bias to threat in children with BI may reduce risk for anxiety disorders. As an important first step, Liu *et al.* test whether attention bias modification (ABM) reduces symptoms of anxiety in children with BI. ABM is a form of cognitive training that implicitly reduces attention to threat and has been shown to have efficacy in reducing symptoms of anxiety.<sup>8</sup>

To address these issues, the authors identified 84 children aged 9 to 12 years with behavioral inhibition. Half of these children were randomly assigned to active ABM, and the other half received placebo ABM. In both active and placebo ABM, participants completed 4 sessions of 160 trials over the course of 1 month in their own homes. At the beginning of each ABM trial, 2 faces appear very briefly on the left and right sides of a computer screen. In the critical trials, one face has an angry expression, and the other face has a neutral expression. After the faces disappear, an arrow appears at one of the 2 locations previously inhabited by the faces, and participants must indicate with a button press whether this arrow is pointing upward or downward. In active ABM, the arrow always appears at the location previously occupied by a face with the neutral expression. The hypothesis is that over time, participants in active ABM implicitly learn to attend to the neutral face when the 2 faces appear, because the arrow always appears at that location. In placebo ABM, participants undergo the same number of sessions, but the arrow appears randomly at

the location of either the angry face (“angry trials”) or neutral face (“neutral trials”). Thus, no attention training takes place in placebo ABM. Before and after training, symptoms of social anxiety and separation anxiety are measured using the Diagnostic Interview Schedule for Children (C-DISC-V). In addition, functional magnetic resonance imaging (fMRI) data were available in a subset of 34 participants as they performed the placebo version of ABM before and after training.

The most important result from the study of Liu *et al.* is that active ABM was associated with a significant reduction in separation anxiety but not social anxiety relative to placebo ABM. This result is compelling because of the use of a rigorous randomized controlled design and a statistical approach that accounts for baseline differences in anxiety and other confounding factors. This study is the first to demonstrate a reduction in symptoms in children at high risk for anxiety disorders on the basis of behavioral inhibition and lays the groundwork for testing whether such interventions can be preventive of anxiety disorders. The most important future direction is to longitudinally follow this sample and to test whether the benefits persist beyond the study period, and, ultimately, whether the intervention can prevent the onset of psychiatric disorders as the children grow older.

An important limitation of the study is that it is powered to provide only a limited view of the neural effects of ABM on children at risk for anxiety disorders. Because of a relatively small sample size for the imaging data ( $n = 34$ ), several methodological decisions were required to maximize power and to reduce multiple comparisons, at the necessary expense of providing a narrower view. First, brain activity is examined in just 3 bilateral a priori–defined regions: the amygdala, insula, and ventrolateral prefrontal cortex (VLPFC). Second, in the primary analysis, the authors operationalize brain activity to refer to activity during neutral trials minus angry trials, and then report differences in this measure for the active versus placebo group. Using this metric, the authors report that training was associated with reductions in activity in the amygdala and insula and activity increases in the VLPFC. This bird’s-eye view of the data did not allow the investigators to determine whether training-related activity changes took place in the active and/or placebo group, or whether activity changes related to angry trials, neutral trials, or both. In addition, examining brain activity over whole trials of ABM combines activity elicited by multiple psychological processes. It is unclear whether brain activity changes are associated with psychological processes that occur when the faces first appear, when the target appears, or both. Moreover, it is not known whether activity changes are related to changes in emotion-specific attention mechanisms, general attention mechanisms, implicit emotion regulation, or other processes.

Precisely determining the specific neural effects of treatments such as ABM is an important next step in the effort to prevent and to treat mental illnesses such as anxiety disorders. Although several prior studies have begun to uncover the cognitive and neurobiological mechanisms of ABM,<sup>9–11</sup> our knowledge remains limited. By elucidating the biological

substrate of ABM, we may be able to devise new treatments that more directly target this substrate and perhaps have larger treatment effects. Insofar as it is possible, future studies should strive to do the following: (1) examine neural activity across the brain; (2) provide detailed examination of brain responses within individual groups and for particular trial types, rather than highly derived measures of activity; and (3) attempt to unpack the mechanisms that are involved in the brain changes. This last point likely will require additional task-based imaging strategies beyond examining activity during ABM, such as during tasks that measure emotion regulation and attentional control. In addition, it is important to understand brain changes taking place in placebo ABM as well as active ABM, because placebo training can be associated with symptom improvements as well.<sup>8</sup>

In summary, this study makes an important contribution to the field—ABM reduces symptoms of anxiety in children with high behavioral inhibition. Although it is too early to recommend routine use of ABM in high-risk samples, this work suggests that further studies are warranted to determine whether reductions in symptoms persist over time. A more ambitious goal is to ascertain whether interventions such as ABM can prevent the abnormal neurodevelopmental cascade and long-term risks associated with anxiety disorders. Because there are likely few risks to ABM, it would not be unreasonable to offer behaviorally

inhibited children ABM at the current time if coupled with other interventions such as parent training and/or cognitive-behavioral therapy. At the same time, this study highlights the challenges associated with understanding the biological mechanisms associated with treatment; overcoming these challenges holds the potential to advance our understanding of psychopathology and to develop new, more effective treatments.

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