Biological Psychiatry

Commentary

Pediatric Anxiety Disorders: Insights From Basic Neuroscience, Development, and Clinical Research

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Challenges confronting research on mental illness might be met by integrating data across basic neuroscience, development, and clinical research. Pediatric anxiety disorders represent one of the few areas where sufficient progress exists to provide a foundation for such integration. This special issue of *Biological Psychiatry* describes neuroscientific, developmental, and clinical discoveries illuminating a path that could initiate a paradigm shift. These discoveries involve research on defensive behaviors; these are behaviors that are deployed when organisms confront perceived dangers. These discoveries also involve research on regulatory behaviors; these are behaviors deployed to modulate the initial defensive response based on previous experiences, current goals, and context. Defensive and regulatory behaviors are considered throughout the special issue as they relate to brain function across species and clinical expression in people at distinct ages.

The special issue reflects research domain criteria principles carving mental illness components into continuously distributed domains spanning normative and pathological areas (1). Research domain criteria encourage multilevel work on these domains, incorporating brain and behavior assessments applicable to developmental samples and targetable with novel therapies attuned to each domain (2). A dimensional, multilevel approach to this special issue unfolds in four sections, each related to defensive and regulatory behaviors. The first section reviews basic science research, followed by a second section on early human brain development and premorbid risk as these processes relate to defensive behavior. The third section describes specific domains of disrupted functioning in children with clinical features of anxiety. The fourth section describes new treatments that target domain-specific disruptions and causally link defensive and regulatory behaviors to clinical end points.

Together, the articles in this special issue leverage basic research in the service of clinical innovation. The fundamental observation arising from this issue is a view of defensive and regulatory behaviors at distinct life stages as reflecting developmentally layered amalgamations. This framework encourages age-specific approaches to classification, risk prediction, and treatment. While the current issue focuses on anxiety, this framework is likely to have broad relevance for other disorders with developmental unfolding, including adult mental illnesses associated with pediatric anxiety. As such, progress in pediatric anxiety might encourage efforts to create broad perspectives that integrate neuroscience, clinical research, and developmental approaches.

Basic Science

The study of anxiety disorders has long benefited from basic science research on defensive behavior. This work has examined how adults respond to threats, learn about threats, and regulate their responses. Much of this work has studied the rodent amygdala and its interactions with portions of the frontal cortex shaping behavior. This research finds that a layering of circuitry responses accrues with development, and Figure 1 shows how such layering of psychological processes highlighted in this special issue manifests in humans.

Three articles on basic science in this special issue delineate dynamic threat-related circuitry development, with lasting imprints of particular environmental influences at distinct developmental epochs. First, Sullivan and Opendak (3) review early amygdala development in rodents, with a focus on the effects of caregiver interactions. The authors highlight a developmental shift in threat response from attachment-related circuitry in very young pups to amygdala-dependent circuitry in older pups. Stress and caregiver adversity can shift the timing of this transition and permanently impact circuitry response to threat. Next, Gerhard *et al.* (4) describe nonlinear development of threat-associated behaviors and circuitry in adolescent rodents, highlighting reduced extinction in adolescents compared with both younger pups and adults. This nonlinearity reflects the increased influence of portions of the medial prefrontal cortex that amplify defensive behavior, coupled with the decreased influence of portions of the medial prefrontal cortex that diminish defensive behavior. Gerhard *et al.* (4) view adolescence as a sensitive period, during which stress exerts larger lifelong impacts on some amygdala circuitry components relative to other developmental epochs. Finally, Kenwood and Kalin (5) describe temperamental variation in defensive behavior in rhesus monkeys. The authors describe how behavior and circuitry function in juveniles with high anxious temperament resemble behavior and circuitry function in children who are at risk for anxiety disorders. The authors further describe how pharmacologically altering amygdala plasticity at specific life stages might initiate long-term changes in drivers of defensive behaviors.

Together, this basic research illustrates how the maturation of early-developing circuitry girds the maturation of later-developing circuitry. As such, each development stage creates distinct combinations of circuits, accrued through new changes occurring on top of older ones. From this perspective, individual differences in the neural correlates of defensive and

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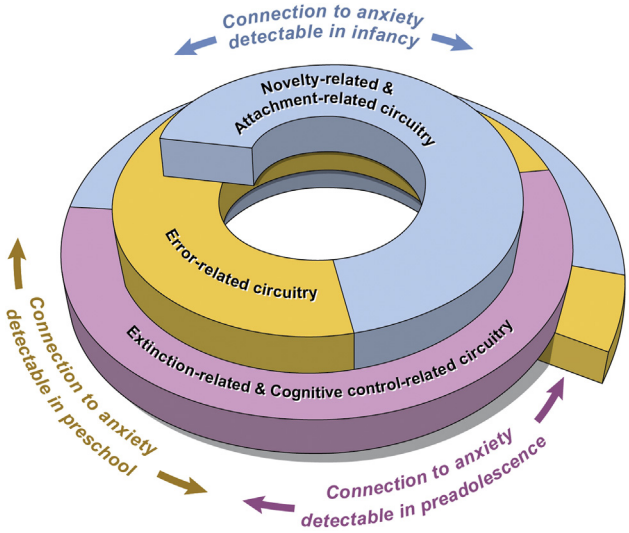

Figure 1. Layering of psychological processes and associated neural circuitry results from graded maturation. Processes at the top of the spiral manifest relations with anxiety earlier than processes at lower levels in the spiral. Layering results when late-maturing processes influence threat responding in tandem with early-maturing processes.

regulatory behaviors involve distinct combinations of circuitry components at each developmental stage. Thus, biomarkers and responses to associated treatments might similarly change in humans.

Human Development

Research finds similar dynamics for risk trajectories in children as found in basic research on defensive behavior. The risk for chronic anxiety manifests during infancy and is expressed through variation in defensive circuitry and behaviors. This risk is modulated at later developmental stages by maturation in regulatory circuits and environmental factors that influence them. For example, circuitry supporting novelty detection relates to defensive behavior among infants, whereas circuitry supporting extinction relates to anxiety in children. As these processes develop, they shape risk for most persistent adult anxiety disorders, expressed as lasting remnants of earlier problems. In humans, like rodents and monkeys, a staged sequence of defensive behaviors arises. This leaves human defensive and regulatory behaviors at each life stage to reflect emergent integrations of established and evolving capacities.

Articles in the second section of this special issue describe principles of early brain development as they apply to anxiety risk trajectories. First, Doyle *et al.* (6) describe aspects of in utero, neonatal, and toddler brain development as well as work that links variation in this early brain development to risk trajectories for anxiety disorders. The authors highlight the first 2 years of life as an intense period of rapid brain growth that initiates progressive changes unfolding over at least the first 2 decades of life. They describe how fetal heart rate variation in utero and amygdala and cortical connectivity at birth may predict behaviors in toddlerhood and the associated risk for anxiety disorders. Fox *et al.* (7) describe similar research on the defensive behavior of infants and preschoolers, focusing on risk prediction well into adulthood. This work examines behavioral inhibition, an early-appearing temperament characterized by increased reactivity and attention to new situations and stimuli. The authors review data confirming a view of behavioral inhibition as a potent risk factor that interacts with later-arising processes to shape risk for anxiety disorders. These later processes support "automatic" and "planful" forms of attention control and their associated neural substrata.

The work in this section converges with basic science research to highlight the importance of early brain development in anxiety disorders. Novelty-responsive circuitry functions at birth, develops in a nonlinear fashion, and relates to risk for anxiety expressed at later ages. At each stage, risk reflects an emergent process that combines accumulating changes in circuits driving behavior and their susceptibility to environmental influences.

Pediatric Anxiety

The third section of this special issue focuses on impaired cognitive and neural circuitry domains in pediatric disorders. Drawing on the themes of preceding sections, articles carve anxiety into multiple interacting components. Many findings are framed in light of the adult literature as it examines components described in the new articles.

Treanor *et al.* (8) review the published literature on threat learning in children with and without anxiety disorders, highlighting the need for methods-based research. The authors conclude that some threat-related disturbances differ in children and adults. In fact, in some cases, the neural circuitry responding in anxious children may appear opposite to the patterns observed in adults. These and other points highlight the need for longitudinal studies mapping the trajectory of such responding and its relation to clinical outcome. Next, Fitzgerald *et al.* (9) review evidence for disrupted cognitive control and associated brain networks, revisiting themes explored by Fox *et al.* (7). Like many articles in this special issue, Fitzgerald *et al.* note how disruptions associated with anxiety differ across age groups. For instance, young children with versus without problematic anxiety appear to manifest decreased error-related brain activity. Older children with problematic anxiety, in contrast, appear to express increased error-related activity, a pattern also seen in adults. Perino *et al.* (10) examine associations of attention with pediatric anxiety in a new empirical study. Their results indicate that increased clinician-rated anxiety is associated with increased attention to nonemotional salient stimuli coupled with increased activity in the brain's ventral attention network. Finally, Peris and Galván (11) review work indicating that adolescence is a time of heightened risk-taking relative to older and younger individuals, associated with increased striatal reactivity to rewards coupled with incomplete maturation of prefrontal circuitry. Children with anxiety disorders may have decreased risk-taking during adolescence coupled with altered activity in striatal and prefrontal regions.

Together, these articles suggest that domains disrupted in adult anxiety disorders have nonlinear developmental

trajectories. Disruptions must be considered in light of normative trajectories that generate patterns in early life that differ from deviations in adults.

Treatment

In the final article, Lazarov and Bar-Haim (12) describe cognitive training approaches that target disrupted information-processing domains. The disrupted defensive and regulatory domains described in basic science studies might be targeted at distinct developmental stages, based on life stages where plasticity is greatest. As such, research in this area extends basic science understandings of age-specific circuitry plasticity and its relation to defensive behavior. To evaluate such potential treatments, the authors outline a three-step pipeline: identifying targets, demonstrating engagement, and implementing target modification. Attention bias modification is furthest along this pipeline, having been shown in meta-analysis to reduce symptoms of anxiety in children. Lazarov and Bar-Haim (12) describe progress currently being made for other treatments.

Conclusions

This special issue integrates basic neuroscience, development, and clinical research. The articles herein highlight variation in nonlinear developmental trajectories of cognitive and brain network domains linked to pediatric anxiety. These variations are best viewed as deviations from normative developmental trajectories. Moreover, this special issue suggests that outwardly similar defensive and regulatory behaviors can reflect different circuit mechanisms at different developmental stages. Specific sensitive periods define developmental windows where environmental influences have particularly profound, enduring impact on developing circuit mechanisms and associated behaviors. The principles afforded by these themes reveal novel opportunities for prevention and treatment.

The articles in this special issue evoke a long-term integrative vision, encouraging prospective studies of children before birth, comprehensively assessed across different domains of functioning. These studies need to define the ways in which deviations differ from normative trajectories while illuminating the factors that drive these deviations and their associations with clinical features of anxiety. Ultimately, new treatments may correct these deviations in ways in which basic science localizes the responsible underlying brain mechanisms. Because developmental plasticity creates opportunities for both potent beneficial and deleterious effects, noninvasive treatments such as cognitive training provide a reasonable starting point for clinical applications of this vision. This integration of basic neuroscience, development, and clinical research also provides a framework for studying and devising treatments for other mental illnesses with developmental precursors.

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Article Information

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