Anxiety, Depression, and Suicide in Youth

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Anxiety disorders and depression are among the most common psychiatric illnesses affecting youth. Anxiety disorders typically begin in childhood, whereas the onset of depression frequently occurs later during adolescence or early adulthood. These illnesses are highly comorbid, with pathological anxiety regularly preceding the development of depression. The lifetime prevalence of anxiety disorders when assessed in adolescents is reported to be as high as 32% (1), whereas the estimated 12-month prevalence of major depression in adolescents is approximately 13% (2). Prior to adolescence, the incidence of these disorders is the same between boys and girls; however, as girls mature and go through puberty, they are approximately twice as likely as boys to be diagnosed with anxiety and major depression. In addition to causing considerable suffering and impaired functioning, when severe, these illnesses can be life threatening. Tragically, 6,200 suicide deaths were reported in 2017 among U.S. adolescents and young adults from 15 to 24 years of age (3), and suicide is the second leading cause of death among individuals 10–34 years of age (4).

As with other psychiatric illnesses, the risks for developing anxiety disorders and major depression are due to interactions between heritable and nonheritable factors. It is estimated that the heritability of anxiety and major depression is between 30% and 40%, leaving a considerable amount of the risk to potentially modifiable environmental factors. Genome-wide association studies with increasingly large sample sizes continue to identify genes that help explain a portion of the heritability for anxiety and depression (5). However, it is important to note that a recent study has provided evidence questioning the validity of previous findings that have linked a number of the familiar, "usual suspect" candidate genes (e.g., polymorphisms of the gene for the serotonin transporter protein) to be strongly associated with anxiety and depression (6). Early life trauma, neglect, inadequate parenting, and ongoing stress are among the environmental factors that contribute to the likelihood of developing anxiety, depression, and other stress-related disorders. Adolescence is a particularly vulnerable period, as the psychosocial challenges of adolescence converge with rapid and substantial developmental changes in the brain and in hormones. Prior to the onset of anxiety disorders and major depression, at-risk phenotypes or personality traits such as behavioral inhibition (7) and neuroticism (8), which are also partially heritable, can be identified and provide an opportunity for developing early intervention strategies for children at risk.

Two now classic clinical trials have evaluated the efficacy of selective serotonin reuptake inhibitors and cognitive therapies for the treatment of major depression and anxiety disorders in youth. The Treatment for Adolescents With Depression Study was a randomized 12-week trial involving 439 adolescents with major depression in which fluoxetine, cognitive-behavioral therapy (CBT), CBT plus fluoxetine, and placebo were compared (9). Results demonstrated that fluoxetine plus CBT and fluoxetine alone were significantly better than placebo, with the combination outperforming fluoxetine alone. CBT by itself did not statistically differ from placebo (fluoxetine plus CBT, 71% response; fluoxetine alone, 60.6% response; CBT alone, 43.2% response; placebo, 34.8% response). With continued treatment, rates of response remained high for up to 36 months (10). The Child/Adolescent Anxiety Multimodal Study was a randomized clinical trial comparing 14 CBT sessions with 12 weeks of sertraline plus CBT, sertraline alone, or placebo in 488 children and adolescents (7–17 years old) with separation anxiety disorder, generalized anxiety disorder, or social phobia (11). Results demonstrated that all therapies were more effective than placebo and that the combination of sertraline plus CBT was superior to the other active treatments (sertraline plus CBT, 80.7% response; CBT, 59.7% response; sertraline alone, 54.9% response; placebo, 23.7% response). Long-term follow-up of 319 of these children revealed that only 22% were in stable remission, whereas the remainder were either chronically ill or had relapsed (12). Taken together, these studies highlight the efficacy of relatively short-term interventions and point to the need for treatments that can fundamentally affect childhood developmental trajectories that will enable initial interventions to have long-lasting positive effects.

Efforts should be devoted to developing treatments that have the potential to positively affect the at-risk neurodevelopmental trajectories of vulnerable children.

In this regard, a more complete understanding of the pathophysiology underlying anxiety disorders and major depression in youth is necessary to advance the development of new early intervention strategies. Neuroimaging studies suggest that anxiety and depression share alterations in the function of prefrontal-limbic circuits that underlie the adaptive regulation of emotion and the processing of anxiety

(13), and studies also show alterations in reward-related processing to be associated with both anxiety and depression (14, 15). However, to move beyond the associations between brain and behavior that have been identified with neuroimaging, preclinical studies are critical to elucidate potential mechanisms that underlie anxiety- and depression-related pathophysiology. For various reasons, developing valid preclinical animal models of depression has been challenging. In contrast, anxiety and fear can be effectively modeled in rodents and nonhuman primates (13, 16), and such research has led to a deep understanding of the circuits, cells, and molecules that are mechanistically involved in mediating adaptive and pathological anxiety. The evolutionary expansion of the primate prefrontal cortex makes nonhuman primates particularly valuable for modeling human anxiety, as the expanded primate prefrontal cortex is prominently involved in mediating internal emotional experiences and cognitive processes that are unique to primate species and that, when aberrant, contribute to psychopathology.

The neural circuitry underlying fear and anxiety includes subcortical structures such as specific amygdala nuclei, the bed nucleus of the stria terminalis, the anterior hippocampus, and brainstem regions such as the periaqueductal gray (17). These subcortical regions, via their synaptic connectivity, work in concert with the ventromedial prefrontal cortex, the anterior insular cortex, the anterior cingulate cortex, and other regions of the posterior orbitofrontal cortex to regulate and process anxiety. In relation to major depression, the presence of anhedonia is a clinical feature that clearly distinguishes depression from anxiety. This diminished capacity to enjoy and engage with one's world is in part mediated by altered function of the brain's reward circuitry. For example, neuroimaging studies in adolescents with depression demonstrate altered reward-related responsivity of various components of this system, including the nucleus accumbens and striatum, as well as cortical regions such as the insular and the anterior cingulate cortices (14).

This issue of the *Journal* focuses on depression and anxiety during childhood and adolescence and importantly includes two articles that address mental health issues in disadvantaged youth living in poverty. We include four research articles that address critical treatment areas, including the use of CBT for treating childhood grief, ketamine for treatment-resistant adolescent depression, the use of neuroimaging in anxious youth to predict treatment response, and a preschool intervention for preventing psychopathology in disadvantaged children. Another article that is relevant to the health of disadvantaged and underresourced populations presents research that combines measures of inflammation with neuroimaging to better understand factors that may underlie physical health problems in children living in poverty. Other articles in this issue are focused on understanding underlying pathophysiology (capitalizing on neuroimaging data from the large Adolescent Brain Cognitive Development [ABCD] database), examining neuroimaging measures associated with suicidal thoughts, and examining reward-related neural processing in relation to disruptive behavior disorders.

Treating Prolonged Grief in Children and Adolescents

The loss of a loved one during childhood is traumatic and increases the risk to develop stress-related psychiatric illnesses such as depression and posttraumatic stress disorder (PTSD). Boelen and coauthors (18) present data from a randomized clinical trial comparing CBT aimed at coping with grief with an intervention employing supportive counseling in 134 children and adolescents who met criteria for prolonged grief disorder. Prolonged grief disorder, which was recently added to ICD-11, is defined by the presence of significant and interfering grief symptoms that last beyond the first 6 months after a loss. Although it is not in DSM-5, prolonged grief disorder is similar to the DSM-5 diagnosis of persistent complex bereavement disorder. In this study, each participant received nine sessions of the respective therapies, and their parents or caregivers received five therapy sessions focused on supporting their children and strengthening their relationship with their child. Results demonstrated that, when assessed at 3, 6, and 9 months posttreatment, both treatments had positive effects. However, the CBT group demonstrated greater decreases in grief symptoms at all posttreatment time points, and at 6 and 12 months, CBT considerably outperformed counseling in the domains of depression and PTSD symptoms. Margaret Crane and Lesley Norris, Ph.D. candidates, along with Dr. Philip Kendall from Temple University, contribute an editorial that speaks to moving beyond the findings presented in this study toward developing personalized treatment approaches for prolonged grief and modifying current treatment strategies to make them more widely accessible to suffering youth (19).

An Intervention in Children Living in Poverty Aimed at Reducing the Later Development of Psychopathology

Poverty is associated with numerous factors that are stressful and traumatic. To assess the extent to which an early school intervention can make a difference for impoverished children, Bierman et al. (20) report data from a randomized clinical trial examining the effects of an evidence-based intervention on the development of psychopathology, when assessed years later during adolescence. In this study, 356 4-year-old children from low-income families received an intervention consisting of a social-emotional learning program combined with an interactive reading program that was compared with usual educational practices. The children were recruited from three counties in Pennsylvania and came from families with a median annual income of $15,000. While differences between the interventions were not apparent when children were in the 7th grade, significant differences were observed when children reached 9th grade. For example, significantly fewer conduct problems, emotional

symptoms, and peer problems were present in the 9th graders who, at 4 years of age, had participated in the social-emotional learning program. This study underscores the need to view the societal issue of poverty as stressful and traumatic, the disparities in health care associated with poverty, and the profound effects poverty can have on families and children. The findings are encouraging, with important public health implications, and clearly support early interventions aimed at promoting healthy social, emotional, and cognitive development in children facing the chronic adversity of growing up in poverty.

Enhanced Linkages Between Neural Activation and Inflammation in Impoverished Children

Miller and coauthors present data from a sample of early adolescents supporting an enhanced association between brain activation and peripheral inflammation that is selective to children living in poverty (21). The findings may shed light onto why underprivileged children have increased vulnerabilities to develop psychiatric and physical illnesses. The study was performed in 207 12- to 14-year-old children from the Chicago area who came from families across the socioeconomic spectrum. To explore a link between peripheral inflammation and neural function, the investigators correlated blood inflammatory markers (C-reactive protein, tumor necrosis factor-α, and interleukins-6, -8, and -10) with functional neuroimaging measures that assessed threat- and reward-related neural activation. First, the authors found that children living in poverty had higher levels of inflammation than children from higher socioeconomic backgrounds. In addition, the results demonstrated that in impoverished children, the inflammatory markers were positively correlated with both threat-related amygdala and reward-related striatal activation. The authors speculate that this enhanced coupling between neural and inflammatory processes may be due to the developmental impact of chronic adversity and may be a mechanism linking poverty to increased stress reactivity and illness. Interestingly, the positive relation between inflammatory markers and striatal activation was not in the predicted direction. Dr. Charles Nemeroff, from the University of Texas at Austin, contributes an editorial that emphasizes the deleterious effects of poverty on poor health and mental illness and further elaborates on the immune and neural alterations found in children who grow up in such impoverished and unfortunate conditions (22).

Neuroimaging Measures Are Not Good Predictors of Childhood Suicidal Ideation and Behavior

Vidal-Ribas and coworkers (23) use the large ABCD multimodal imaging database to comprehensively assess the usefulness of structural and functional brain measures in predicting childhood suicidal thoughts and behaviors. In a sample of 7,994 9- to 10-year-old children, the researchers found that 14.3% of the sample, or 1,140 children, had suicidal ideation or behaviors as reported by themselves or by caregivers. The occurrence of suicidal thoughts and behaviors was associated with increased levels of psychopathology and psychosocial adversity. Of the more than 5,000 statistical tests that were performed with multiple imaging measures (to assess cortical thickness, resting-state functional connectivity, and task-related functional activation), only one test survived correction for multiple comparisons. This finding revealed a relation between reduced thickness of the left bank of the superior temporal sulcus and caregiver-reported suicidal thoughts and behaviors. The authors draw the conclusion from these overall negative findings that current neuroimaging methods are not useful in reflecting the biological underpinnings of suicidal ideation and behavior in youth. In their editorial, Dr. Randy Auerbach from Columbia University and Drs. Henry Chase and David Brent from the University of Pittsburgh discuss the comprehensive and thorough nature of the study, the potential meaning of the superior temporal sulcus finding, and other critical aspects worth considering in future studies aimed at understanding the factors underlying youth suicide (24).

Reward-Related Functional Brain Alterations in Children With Disruptive Behavior Disorders and Callous-Unemotional Traits

Hawes et al. examine the extent to which children with disruptive behavior disorders (DBDs) (e.g., oppositional defiant disorder and conduct disorder) have alterations in neural responses to the anticipation and actual receipt of a reward (25). As in the Vidal-Ribas et al. study (23), these investigators used the ABCD neuroimaging database to provide a large sample size. Alterations in reward processing characterized by difficulties in delaying gratification and overvaluation of immediate rewards have been hypothesized to underlie externalizing phenotypes. In this study, reward-related brain activation in response to a monetary incentive delay task was examined in youth with DBDs who were subdivided into those with DBDs only (N=276) and those with DBDs with callous-unemotional traits (N=198), a characteristic that is more likely to be associated with antisocial behavior. The data from these children were compared with neuroimaging data from 693 typically developing youth. The children were, on average, 9.5 years old when studied. The findings from the study demonstrated that regardless of the presence of callous-unemotional traits, youth with DBDs exhibited decreased dorsal anterior cingulate activation in response to reward anticipation and increased orbitofrontal cortical and nucleus accumbens activation during reward receipt. Some neural activation differences between the DBD-only group and the DBD callous-unemotional trait group were also observed. Taken together, these findings shed light on the cortical control systems and subcortical reward-related neural substrates that may underlie the maladaptive behaviors characteristic of youth with DBDs.

Pretreatment Reward-Related Brain Activation Is Associated With Response to Psychotherapy in Youth With Anxiety Disorders

Sequeira and coworkers (26) explore the use of pretreatment functional imaging measures to predict treatment responses to psychotherapy in 9- to 14-year-old children with anxiety disorders (i.e., separation anxiety disorder, generalized anxiety disorder, or social anxiety disorder). Similar to other articles in this issue, this study probed reward-related brain activation. In this case, activation of brain regions encompassing the medial prefrontal cortex and the striatum was compared between the conditions of winning a reward relative to the experience of losing. The study included 50 children treated with 16 sessions of CBT, 22 children treated with child-centered therapy, and 37 healthy comparison youth. The intervention was effective, as 67% of the patients, regardless of treatment, responded to the intervention. Prior to treatment, greater activation of the medial prefrontal cortex was found in the patients with anxiety compared with the control subjects. However, the authors note that this difference in medial prefrontal activation could be accounted for by the co-occurrence of depressive symptoms in the anxiety group. Importantly, the authors found that as a group, treatment responders compared with nonresponders had increased pretreatment activation of regions encompassing the subgenual anterior cingulate cortex and the nucleus accumbens. These initial findings point to the potential importance of understanding reward-related brain systems in relation to psychotherapeutic outcomes in youth with anxiety. The authors speculate that increased striatal responsivity to rewards prior to treatment could be associated with increased motivation and engagement with therapy.

A Proof-of-Concept Trial Assessing Ketamine for Depression in Adolescents

Dwyer and colleagues (27) report the results of a small randomized double-blind single-dose crossover study in 17 adolescents with major depression who had not responded to at least one adequate trial of an antidepressant. In this trial, intravenous ketamine (0.5 mg/kg) or intravenous midazolam (0.045 mg/kg) was administered to each patient in a crossover design with a 2-week interval between treatments. Patients remained on their current psychiatric medications throughout the study. Sixteen patients completed both treatments, and the primary outcome was depression severity measured with the Montgomery-Åsberg Depression Rating Scale (MADRS) 24 hours after the infusion. Results demonstrated that 24 hours after infusion, ketamine had a significantly greater effect than midazolam in reducing depressive symptoms. For the midazolam infusion, the average pretreatment MADRS score was 31.88, and 24 hours later it was 24.13. For the ketamine infusion, the average pretreatment MADRS score was 30.56, and 24 hours later it was 15.44. Responders were defined by a 50% reduction in the MADRS score, and it was found that ketamine was associated with a response in 77% of the patients, with 35% of patients responding to midazolam (five of six of these participants also responded to ketamine). Compared with midazolam, the ketamine infusions were associated with reduced MADRS scores at all time points measured up to 14 days postinfusion. Ketamine was associated with dissociative side effects that were transient as well as with transient changes in blood pressure and heart rate. In their editorial (28), Drs. Parikh and Walkup from Northwestern University discuss the potential importance of this finding in relation to treating adolescent depression, but they also put into context such issues as the small sample size, the difficulty maintaining blinding because of ketamine's dissociative effects, and concerns raised by others regarding the role of opiates in mediating ketamine's effects in relation to its addiction potential (29).

Conclusions

Many psychiatric disorders have their origins early in life, which is clearly the case with anxiety and depression. In addition, the adolescent transition period is a time of increased risk during which psychiatric illnesses, especially depression, tend to emerge. Although there are adequate treatments for youth with anxiety and depressive disorders, many individuals do not respond to current treatments, and it is important to emphasize that many young people with psychiatric illnesses do not have access to available treatments. There is no question that we need better treatments and better access for children suffering from these disorders. This issue of the *Journal* highlights recent insights and clinical advances related to the treatment of anxiety disorders and major depression. Findings with the potential to directly affect the clinical care of youth include: demonstration of the efficacy of CBT in treating prolonged grief; early school socioemotional and cognitive interventions in disadvantaged children that prevent adolescent psychopathology; the rapid efficacy and safety of ketamine in reducing depressive symptoms in youth with treatment-resistant depression; and the promise of using functional neuroimaging to inform treatment choice and predict outcomes in youth with anxiety disorders. Other articles in this issue address pathophysiology, demonstrating increased coupling between brain and peripheral inflammatory markers in impoverished youth, altered reward-related brain activation in youth with DBDs, and a lack of association between structural and functional neuroimaging measures with suicidal ideation and behavior in youth. Continued research focused on a better understanding of the mechanisms underlying the early life risk to develop anxiety disorders and major depression is critical for the development of novel, improved treatment strategies. Efforts should be devoted to developing treatments that have the potential to positively affect the at-risk neurodevelopmental trajectories of vulnerable children. Such early life interventions provide the hope of

moving beyond symptomatic treatment and toward prevention strategies.

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