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Review article

## Reducing the Burden of Depression in Youth: What Are the Implications of Neuroscience and Genetics on Policies and Programs?

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 A B S T R A C T

Mood disorders are a leading cause of the burden of disease in youth. Three critical lessons emerge from the reviews in this issue that are relevant to our understanding of these common mental disorders: first, that the brain is in a highly dynamic stage of its development during youth; second, that environmental factors interact with genetic factors to influence the probability of risk behaviors and dysphoric states; and third, that shared developmental and genetic factors may account for the bulk of emotional and behavioral outcomes in youth, and that environmental influences may affect the specific expression of the phenotypes associated with these pathways. Although this evidence does not immediately indicate the potential for new interventions, it is consistent with current policy and practice recommendations. Interventions should focus on both improving the early detection and management of depressive disorders as well as preventive strategies that aim to train children and youth to improve cognitive control and manage stress more effectively. Limiting access to harmful risk-taking situations and providing opportunities to engage are less harmful, but equally exciting, alternatives in a pragmatic universal prevention policy option. Key research priorities and paradigms emerge from this evidence, particularly in the context of the grand challenges in global mental health.

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Mental disorders, such as mood disorders, substance use disorders, and psychoses, are the leading cause of ill health in adolescents and young people (referred to as “youth” in this article) globally, including in low- and middle-income countries (LMIC) [1]. Even in sub-Saharan Africa where HIV remains a major cause of ill health in this demographic group, mental disorders are the leading noncommunicable cause of disease burden. Additionally, mental disorders underlie a substantial proportion of suicides, a leading cause of death in youth [2]. Apart from causing enormous suffering in youth, the majority of mental disorders seen in adults have their onset in youth. Thus, youth may represent the most important demographic window for interventions to reduce the burden of mental disorders across the life span. This article will principally address mood disorders because these contribute the most to the burden of disease. Although not explicitly addressed, some of the policy and prac-

tice considerations raised in this article apply to other disorders as well. Substance use disorders are also addressed in another article in this issue [3].

The terms “mood disorder” and “depressive disorder” tend to be used interchangeably; furthermore, the term “depression” is used both to indicate an emotional state and a mental disorder. Although transient situational depression is a common emotional state among youth, the persistent disruption of affect characteristic of depressive disorder, is less common. Although rare before puberty, the prevalence of depressive disorder increases dramatically after puberty, with a notable gender gap—women are between 1.5 and 2 times more likely to be diagnosed, a gap that persists through the life course. A major challenge is distinguishing the point when feelings of sadness and losing interest, along with their behavioral and physical features (such as sleep problems, tiredness, loss of appetite, aches and pains in various areas of the body, and so on), become a “disorder.” Current classifications of mental disorder rely on the number, duration, and impact of these experiences to make this distinction [4]. This method, while being inevitably arbitrary, remains the only

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reliable method currently available as, despite the abundance of research reviewed in this issue, we remain a long way from a valid and replicable biomarker of this disorder.

### Current Recommendations

Youth is a critical period in an individual's life when he/she establishes personal identity, completes education, gets a job, and establishes romantic partnerships. A depressive disorder can derail that trajectory. Despite the rich evidence base on the epidemiology of depressive disorder in youth, we know comparatively less about its causes and treatment. The evidence in support of antidepressant medication is equivocal [11]; in contrast, the evidence pointing to the beneficial effects of brief structured psychological treatments is more robust, including trials from LMIC [5,6]. One notable addition to this rule is the Treatment for Adolescents with Depression Study [7], which reported that a combination treatment using an antidepressant (fluoxetine) and psychological treatment (cognitive-behavioral therapy) was superior to either treatment alone.

In general, current guidelines, including the latest World Health Organization guidelines for the treatment of mental disorders in general health care settings, advocate the use of psychological treatments as the first line of treatment for depressive disorder in youth, with judicious use of fluoxetine reserved for nonresponders [8]. A major barrier to delivering such treatments is the lack of skilled mental health human resources and youth mental health services globally. A key strategy to address these barriers is task sharing of specific mental health interventions (e.g., a specific psychological treatment) to lay and community health workers in collaboration with specialists. Such models of care have been shown to be extremely effective in improving recovery rates in trials in LMIC [9]. There is modest evidence supporting preventive interventions to reduce depressive symptoms in children and youth; these are often school based, target those who have subclinical symptoms, and comprise a range of strategies, from programs targeting competence training and social and coping skills to more specific preventive strategies for depression, such as cognitive restructuring [10]. One example of an extensively evaluated intervention is the Penn Resiliency Program that aims to change cognitive distortions and to improve coping skills in children with depressive symptoms; it remains one of the few preventive interventions to have been evaluated in an LMIC [11].

### Lessons From Neuroscience and Genetics

Three critical lessons emerge from the reviews of this issue: first, that far from being a relatively static organ, the brain is in a highly dynamic stage of its development during youth; second, that environmental factors interact with genetic factors to increase, or decrease, the probability of risk behaviors and dysphoric states; and third, that shared developmental and genetic factors may account for the bulk of emotional and behavioral outcomes in youth, and that environmental influences (such as gender roles) may influence the specific expression of the phenotypes associated with these pathways. The dynamic state of the brain is exemplified by the evidence that synaptic pruning is "highly specific and pronounced" during youth, and this is essential for the "rewiring of the brain into the typical adult pattern." Myelination "escalates, speeding information flow and magnifying its impact" (Spear). There is delayed maturation of the pre-

frontal and other frontal regions, which are responsible for the control of subcortical regions; this is associated with immature cognitive control, attentional regulation, response inhibition, and other advanced cognitive functions. There are notable differences in the response of the brain to stimuli in youth and adults; for example, youth brains appear to be less harm avoidant because neural responses to negative feedback may mature later. Rational decision making appears to reach adult levels by mid-adolescence, but this capacity is reduced under emotionally charged circumstances, a phenomenon called "hot cognitions" (Spear); interestingly, it appears that environmental influences, such as social peers, seem to be particularly effective in inducing "hot cognitions," and such states may also be related to an increased risk of using drugs (Potenza). Although most evidence in support of plasticity is from animal research, there is good reason to believe that the brain does respond through anatomical changes in response to environmental stimuli well into adulthood; thus, some synaptic pruning and the formation of new neurons in specific brain regions may be experience dependent. Genetic research also offers an opportunity to better understand the etiology of depressive disorders. However, at best, the heritability of mood disorders does not exceed 40%; this clearly indicates the strong role of environmental factors, both biological (such as hormonal changes associated with puberty) and social (such as gender roles), in explaining individual differences in the risk of depression.

### Implications for Programs and Policies

A range of terms, such as volatile, temperamental, moody, or irritable, has been used to characterize the typical pattern of mood and behavior of adolescents and youth. All of them suggest that emotional dysregulation is characteristic of this period of the life course. The evidence reviewed in this issue greatly contributes to our understanding of the basis of such dysregulation and, potentially, the etiology of mood disorders. Put simply, youth "moodiness" may be best understood as a natural accompaniment of neurodevelopment that can be profoundly modulated, in both enabling and damaging ways, by a range of internal and external environmental factors. Some degree of sensation seeking and risk taking is normative, rational, and even, one may argue, an evolutionary imperative. After all, are not the learning tasks essential for adulthood reinforced by taking risks? The most important policy imperative is to identify how these essential normative tasks can be completed successfully in the rapidly changing environments facing the adolescent brain, rather than emphasizing their control or suppression. Furthermore, the apparent comorbidity of many youth risk behaviors may be explained by their shared genetic and neurodevelopmental origins; differential phenotypic expression may be the result of environmental influences. The curious gender differences observed in the form of higher risk of mood disorders in young women and the higher risk of addictive disorders in young men may well be due to such interactions.

Having said this, there are many unanswered questions regarding the nature of brain development and other biological changes during youth and how they interact with the environment to influence the risk and course of depressive disorders. The road toward translating exciting discoveries in genetics and neuroscience into practical interventions is still a long and uncertain one. In particular, the prospect of answering these questions remains hampered by the lack of a definitive biomarker or endo-

phenotype, such as has been proposed for addictive disorders (Potenza), for mood disorders. These have been recognized among the grand challenges to address the global burden of mental disorders [12]. Advanced methods to investigate brain functioning, for, example, neuroimaging, may offer a new approach for the detection of youth at risk of developing a depressive disorder; such techniques may also be useful to investigate the biological impact of evidence-based treatments and to help develop treatments that can more effectively target the biological processes that predispose to high-risk behaviors. However, it is equally important to investigate the environmental factors that contribute toward resiliency; even though mental disorders are a leading cause of the burden of disease, most youth, including those who live in circumstances of great disadvantage in low-resource countries, are in good mental health [13]. Factors such as peer relationships, parenting practices, and educational attainment are critically important determinants of mental health, and future research should elaborate the role of these factors in influencing risk and gene expressions. It is also important to recognize that there has been almost no research from LMIC that can contribute to the necessary knowledge, and it is unlikely that gene/neurodevelopment–environmental interactions will be illuminated by researching only a tiny fraction of the global population.

In the context of the evidence reviewed in this issue, it is not possible to make any definitive recommendations for new interventions. However, the evidence base is consistent with current policy and practice recommendations. During youth itself, interventions should focus on both improving the early detection and management of depressive disorders based on existing evidence derived from clinical research. Preventive strategies that aim to train children and youth to improve cognitive control and manage stress more effectively may help reduce the propensity for “hot cognition.” Such interventions should be provided in youth-friendly settings, including schools. Limiting access to harmful risk-taking situations and providing opportunities to engage are less harmful, but equally exciting, alternatives in a pragmatic universal prevention policy option. In addition, it is time to move from an outcome-based approach to researching etiology to examining how shared genetic predispositions and neurodevelopmental trajectories interact with environmental factors to lead to differential phenotypes of dysphoria and risk

behaviors in youth. To achieve this ambitious goal, we need to establish large population-based cohorts of young children, with explicit interdisciplinary leadership, in diverse sociocultural contexts. Only then will the promise that an integrative framework of genetics, neurodevelopment, and environment can deliver tangible goods to reduce the burden of mental disorders become a reality.

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