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Risk and Resilience in Extraordinary Times

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In September 2019 we were invited to compile a special issue of *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging* on the topic of neuroimaging risk and resilience. Whatever resilience meant to us in the fall of 2019, it means something entirely different now. Worldwide, the impact of the global COVID-19 pandemic has shuttered schools, childcare centers, restaurants, and businesses. Nowhere has the impact of this virus been more widespread than in the United States, which as of December 2020 had 4% of the world's population but 24% of the world's confirmed COVID-19 cases and approximately 19% of the world's coronavirus deaths (1). As a nation, we have undergone one of the most tumultuous times in modern history. Americans are besieged with a trifecta of existential threats: an uncontrolled pandemic, climate change ravaging the country with fires and floods, and horrifying police brutality toward black and brown people that has cast a harsh spotlight on the systemic racism that pervades every component of our society. This latter issue led the American Medical Association to declare systemic racism an urgent public health threat (2), and the impact of systemic racism on mental health in particular is profound (3). At the same time, the COVID-19 pandemic is overwhelming our hospital systems and has already led to the tragic deaths of >340,000 Americans (1). Frontline health care workers have been stressed in unimaginable ways, working extremely long shifts sometimes with minimal personal protective equipment owing to the failed national response to this pandemic. Further compounding this trauma is social isolation, as these heroic health care professionals must stay physically apart from family and friends to avoid exposing them to the virus. Whatever burnout meant to us collectively in 2019, it means something different now.

Since March 2020, mental health needs in the United States have increased dramatically, with more than one third of adults in the United States reporting anxiety during the pandemic, a threefold increase from the previous year (4). Of the more than 11 million Americans who have been infected with the COVID-19 virus, a large proportion (“COVID long-haulers”) face a long and arduous recovery, with long-standing symptoms of extreme fatigue, weakness, shortness of breath, and other poorly understood neurologic symptoms being common (5). Millions more have faced heartbreak due to the death of loved ones,

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made particularly wrenching by the inability to visit them in their last days due to exposure concerns. We are experiencing these events in isolation; we cannot celebrate major life events like weddings and funerals together. We cannot hug or touch people outside of our households without fear of infecting them or ourselves. These things collectively take a toll on our humanity and our mental health (6). For those who experience domestic violence or child abuse, being confined to the home is both risky and immensely stressful (7). The shuttering of our schools and workplaces has taken a particular toll on young women, who shoulder a disproportionate burden of caring for young children and for elderly parents (8). This will have far-reaching consequences for advancing women's leadership in multiple segments of the workforce. Children and adolescents may be under unique stress (9), as they are being deprived of critical peer interactions and opportunities for exploration during the time when humans are most wired to seek out and respond to social contact and information (10). In addition, in many cases youth are being deprived of educational opportunities, given the inequitable distribution of resources and minimal support for remote learning in our society. We as a species are not equipped to deal with this kind of chronic, continuous, multifaceted stressor. There is now—finally—a light at the end of the tunnel with the development of novel vaccine technologies for SARS-CoV-2, the virus that causes COVID-19. But the “next wave” of this pandemic's impact—the mental health crisis rent by both the virus itself and its economic impacts—will have long-lasting, rippling effects on society and has not yet seen its peak. The impact of this collective experience will be felt for decades, if not longer.

It is in this broader societal context of 2020 that the articles in this special issue were conceived and written. Given the unique challenges this period in history presents for adolescents, we hope that the collection of articles in this issue can serve to demonstrate the complex and multifaceted factors that impart both risk for and resilience to mental health outcomes in adolescents in other contexts. Adolescence is a special period that carries its own vulnerabilities but also its own strengths. The work here may be leveraged as a theoretical toolbox to highlight potential avenues through which we might meet the demands of the current situation. Throughout these articles, several themes emerge, as highlighted below.

An overarching theme of several articles in this issue is the critical role of early-life stress, adversity, and trauma in risk for mental illness, as well as factors that may serve to protect against nonoptimal outcomes. For example, DeRosse and Barber (11) review the neurobiological impacts of early-life stress on the function of emotion and reward circuitry, disruptions of which are hypothesized to lead to development of psychotic symptoms via disrupted stress-related neuro-circuitry, particularly the hypothalamic-pituitary-adrenal axis. Given the highly variable outcomes of youth exposed to early-life stress, however, such literature also provides a window into potential resilience factors: in particular, the potential buffering effects of adaptive changes in reward circuitry and emotion regulation strategies. A review of the evidence from animal models by Tryon *et al.* (12) reveals important insights into the overlap between the brain's response to stress and to traumatic events. Notably, the developmental timing of trauma may have relevance for its impact on the brain and subsequent outcomes. However, the dynamic adolescent brain, as well as the unique

social and family environments of adolescence, may also provide special opportunities for resilience.

A second theme is that of risk and resilience in vulnerable populations. Several factors impact risk in typically developing youth, but in vulnerable youth, risk factors may be enhanced or may be entirely distinct. A set of articles in this issue explore the ways in which children and adolescents with different profiles of vulnerability (psychosis, autism spectrum disorder, neurogenetic disorders, and sexual gender minority status) may experience risk or find resilience. First, in youth at clinical high risk for psychosis, Vargas *et al.* (13) highlight the importance of conceptualizing resilience outside of dichotomous outcomes (conversion to overt psychosis vs. nonconversion). They also raise the possibility of “skin-deep resilience,” whereby apparently resilient outcomes in the face of adversity, i.e., better self-control/executive function, may co-occur with risk factors for long-term adverse health outcomes, suggesting that a resilient “outward face” can exert a toll on physical health. Hamilton *et al.* (14) further explore risk in clinical high risk youth with a focus on using electrophysiological measures to identify predictors of conversion to psychosis as well as predictors of remission. Next, Forbes *et al.* (15) consider the critical interplay of social threat experiences and neural social affective systems in the developmental pathways to risk or resilience to depression in the context of sexual and gender minority adolescents, a uniquely vulnerable population. This socially and developmentally informed clinical neuroscience model sheds light on resilience as a dynamic and adaptive process. This point is further emphasized by Molnar-Szakacs *et al.* (16) in the context of neuroimaging-based biomarkers of risk and resilience in autism spectrum disorder. They make the important point that resilience is dynamic and that positive adaptation in one domain may not translate to another domain. The authors advocate for research that focuses on enhancing the resilience factors most likely to have a substantial impact on quality of life. Finally, Jalbrzikowski (17) discusses risk and resilience in the context of a neurogenetic disorder (22q11.2 microdeletion syndrome) that confers elevated risk for neuro-psychiatric outcomes. Notably, environmental factors such as higher socioeconomic status are associated with better psychological functioning in 22q11 microdeletion syndrome. In other high-risk groups, modifiable social factors such as better-quality peer relationships and greater parental warmth contribute to resilience to psychopathology and thus present potential intervention targets for increasing resilience in the context of high-penetrance genetic risk factors.

In the final theme, the issue explores what opportunities we may have to modify or increase resilience. While many of the factors that might impart resilience discussed thus far are inherent aspects of an individual, such as differences in brain structure and function, or stress reactivity, or emotion processing, it is also of great interest what factors we may be able to have an impact on to foster resilience. For example, Belcher *et al.* (18) review the evidence that physical activity, exercise, and aerobic fitness are modifiable resilience factors that operate through strengthening of large-scale neural circuits to improve neural substrates underlying self-regulation. In their review, Méndez Leal and Silvers (19) highlight that adolescence—as a dynamic period characterized by heightened plasticity, “pubertal recalibration,” maturation of neurobiological circuitry relevant to self-control and emotion regulation, and sensitivity to the social environment—may be a particularly opportune window for intervention to promote resiliency to early-life adversity. Finally,

Gee (20) discusses the contribution of multiple levels of interacting systems in society to an individual's capacity for resilience. Supporting this notion, intervening at the family, community, or broader societal level is often most effective for enhancing individual resilience. Longitudinal developmental neuroscience is key for delineating neurobiological mechanisms by which key protective factors or interventions can promote resilience among youth exposed to adversity and identifying targets for intervention. Taken together, this set of articles takes the empowering perspective that poor outcomes are not always foregone conclusions, and that particularly in adolescence there may be unique factors that may make this a special period of resilience and possibility.

The multivariate approaches to the constructs of risk and resilience represented here lead us to ask, "What does it mean to be resilient?" To date, resilience has been largely conceptualized as an inherent quality of an individual: when undergoing (apparently) equivalent stressors, some will "overcome" and others will experience adverse consequences. From a neural standpoint, resilience can be viewed as adaptive brain responses associated with positive outcomes, despite the presence of similar risk factors (21). That being said, we wish to highlight the importance of conceptualizing resilience not as a hardwired trait but instead as something dynamic and bidirectional, with a significant contribution of the collective environment and context in which an individual lives. In some ways, our cultural concept of resilience has been "Americanized" to imply pulling oneself up by one's bootstraps. But perhaps it is time to move on from the glorification of rugged individualism and acknowledge the important role of social support and social context in the possibility for a given individual to have a "resilient" outcome. It is also important to acknowledge that there are factors (genetic, societal, and environmental) beyond one's control that may contribute to nonoptimal outcomes. This theme emerges repeatedly across the work presented here; we know that this kind of social and community support is critical for all of us, and it may be particularly crucial for helping adolescents weather the storm.

Our society is in the process of discovering the promises and boundaries of its own resilience, and we can find inspiration in what we know about the strengths of the vulnerable individuals who have already had to be resilient for so long. We have, over the course of this year, found new ways to connect to and to support each other. There is hope to be found in the mass social uprisings that have occurred in the face of injustice, in the extraordinary efforts of scientists across the world to rapidly develop novel treatments and vaccines for COVID-19, and in the collective efforts and rapidly developed new social norms established to support and protect each other during these difficult times. How the shared events of these times will ultimately be reflected in changes in our brains, and what the long-term impacts of those changes are, is unclear. And whether we can collectively work together to achieve resilience as a community and a species remains to be seen, but as we see the sun set on 2020, we are dramatically and forcefully reminded that we must try.

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