Commentary

Introduction to Special Issue on COVID-19 and Mental Health

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It is somewhat cliché to note that the COVID-19 pandemic has been a life-changing experience for societies across the world, though it is true nonetheless. For many countries, the need to significantly modify both personal lives and the operation of workplaces, schools, and social interactions created unprecedented disruptions that wreaked havoc for many and elicited a variety of emotional responses, including increases in anxiety, depression, and social isolation. However, as much as we all wish that this pandemic was not occurring, it offers a compelling experiment of nature that is allowing researchers across the globe to better understand and identify the host of factors that drive variation in response to stressors, including environmental, genetic, neural, and psychological elements. A large body of research has tried to understand the risk factors that modulate responses to life stressors. However, much of the prior work has been hampered by two factors: 1) the variability and idiosyncrasy across individuals in the types and timings of experienced stressors and 2) the difficulty in obtaining prospective assessments of risk factors in a sufficiently large number of individuals who will subsequently experience stressors so as to determine relationships. The impact of the COVID-19 pandemic was to some extent simultaneous across many individuals within and across societies, and numerous nimble and creative researchers quickly pivoted to confront this experiment of nature. These scientists have used previously acquired or ongoing prospective data collection to develop robust and compelling tests of theories about pre-existing factors that modulate responses to major stressors. Many have also quickly shifted to add new assessments to ongoing studies to address such critical questions. This special issue of *Biological Psychiatry: Global Open Science* brings together complementary and converging results of this research to illustrate both novel insights and strong confirmations and replications of previous findings in regard to our knowledge of the "who, how, and why" drivers of both adaptive and maladaptive responses to major life disruptions and the causes of mental illness. In addition, the accompanying commentaries serve to put this work in context, pull out the key findings, and identify the critical next steps in using this information to move forward our ability to both enhance resilience and treat psychopathology (1–3).

Several studies in this special issue provide confirmation and support for psychological and even neural factors that have been thought to confer risk for greater psychopathology in response to stress. For example, echoing prior work showing that pre-existing mental illness exacerbates responses to stressors, Porter *et al.* (4) found that children with pre-existing mental health difficulties experienced worse well-being during the pandemic. In addition, both Holt-Gosselin *et al.* (5) and Weissman *et al.* (6) demonstrated that adults and youths who reported using more maladaptive coping strategies prior to the COVID-19 pandemic were more likely to have increased internalizing symptoms during the pandemic.

The studies in this special issue also highlight the ways in which variation in brain structure and function prior to the pandemic may relate to stress vulnerability, a unique opportunity to identify neural predictors of adaptive versus maladaptive stress responses. Holt-Gosselin *et al.* (5) demonstrated that reduced insula thickness, a brain region thought to be central to processing and reactivity to emotionally evocative experiences, was related to greater anxiety during the pandemic. Weissman *et al.* (6) found that higher amygdala activation to putatively neutral faces was associated with greater internalizing problems during the pandemic, potentially suggesting augmented sensitivity to negative stimuli. Perica *et al.* (7) found that stronger connectivity between the posterior hippocampus and the anterior prefrontal cortex (or what could be characterized as reduced anticorrelations between the anterior prefrontal cortex and hippocampus) pre-pandemic was associated with greater worry and COVID-19–related stress. This finding is consistent with prior work suggesting that a reduction in the inverse connectivity between the prefrontal cortex and the hippocampus, potentially reflecting top-down regulation of stress responsivity, is associated with greater internalizing symptoms (8).

In complementary work, Miller *et al.* (9) found that stronger connectivity between the basolateral amygdala and the subgenual anterior cingulate cortex pre-pandemic was associated with greater depression both prior to and during the pandemic, with the pandemic depression relationship holding even when controlling for pre-pandemic depression. Given the putative role for these regions of the amygdala and the cingulate cortex in aversive learning and responding, stronger connectivity may be reflective of greater maladaptive integrative of COVID-19–related stress and fear. In addition, Riesel *et al.* (10) showed that greater electroencephalography responses to both errors and correct trials on an inhibitory control task, characterized as increased performance monitoring, were associated with a greater perception of risk from COVID-19. This heightened risk perception in turn mediated relationships to increased anxiety, depression, and obsessive-compulsive symptoms during the pandemic compared with pre-pandemic. This finding complements the large body of literature linking increased performance monitoring and stronger error-related negativity responses to greater risk for anxiety (11). Together these

studies provide novel prospective evidence that variation in a range of indices of brain structure and function may index pre-existing vulnerabilities that contribute to likelihood of the emergence of mental health challenges in response to significant stressors. While these data do not yet suggest that these neural predictors offer clinically actionable indicators of risk, the findings highlight the need to better understand how and why these neurobiological features confer vulnerability versus resilience.

The work in this special issue also illustrates the complex relationships between infection, inflammation, immune responses, and the development of psychosis [12–14]. There are several theories suggesting that inflammation plays a critical role in the development of many forms of mental illness, including speculations about its role in psychosis. As such, Oh et al. [15] demonstrated a relationship between COVID-19 infection severity and the occurrence of psychotic experiences in a large online sample of university students. However, critically, that relationship seemed to be accounted for by the association of anxiety and depression with COVID-19 infection severity, potentially echoing the previous findings of relationships between the severity of internalizing symptoms and psychotic-like experiences [16,17]. Intriguingly, the work by Hatoum et al. [18] also shows similarly complex relationships between genetic risk factors for cannabis use disorders and vulnerability to COVID-19 hospitalization, though these data did not indicate evidence for any direct causal effects of genetic risk for cannabis use disorder on COVID-19 hospitalizations.

Of course, although I describe the pandemic as having a negative impact on many people at the same time, we also know that there is huge variability in the sociodemographic circumstances of individuals and the ways in which the pandemic impacted their lives. The work presented in this special issue confirms this variability. For example, Weissman et al. [6] report the not surprising but nonetheless important finding that youths who experienced more pandemic-related stressors (e.g., sick family members, family financial disruption, family members on the front line, social isolation) were more likely to show increases in depression and anxiety during the pandemic. Relatedly, Stinson et al. [19] reported that children with a greater history of adverse childhood experiences pre-pandemic had worse mental health during the pandemic and greater COVID-19–related stress. In addition, Asian, Black, and multiracial youths reported greater COVID-19–related stress and discrimination compared with non-Hispanic White youths, though race and ethnicity did not modulate the relationship between adverse childhood experiences and pandemic mental health or worry. Also, Zebley et al. [20] provided strong evidence for the toll that COVID-19 is taking on our health care workers, illustrating the high rates of anxiety and depression that remained significantly distressing even 6 months after the initial assessment. As we might predict, risk factors for greater depression and anxiety during the pandemic among COVID-19 health care workers related to their personal experiences with friends and family experiencing COVID-19, social isolation, financial and child care stress, and their own fears of contracting COVID-19 and direct exposure to patients with COVID-19.

The findings in this special issue also show variability in the degree to which individuals within families converged or diverged in their emotional responses to the pandemic. For example, Porter et al. [4] found that parents' mental health responses to the pandemic were strongly related to their children's mental health responses. However, there was also evidence for divergence. Specifically, Carroll et al. [21] provide what may be the first behavioral genetic twin design study examining gene-by-environment interactions in response to a natural disaster. Their novel and important findings illustrate that the occurrence of the pandemic actually augmented individual nonshared environment contributions to both emotional symptoms and conduct problems in youth relative to shared familial environment and genetic contributions. While these results are consistent with bioecological models that suggest that stress augments and amplifies environmental contributions, the finding that it was more so for nonshared child-specific experiences rather than shared familial experiences has critical implications for how we think about designing more person-specific interventions for shared stressors.

COVID-19 has had a dramatic impact on mental health across the world, both because of the direct effects of the virus on various facets of brain and immune function and because of the effects of economic, social, and lifestyle disruptions. The intriguing findings illustrated in this special issue begin to parse how and why some of these effects are occurring, how they differ across individuals, and how they related to pre-existing vulnerabilities. The results also identify some potentially actionable pathways for prevention and intervention that may be relevant to other types of stressors and negative life events that individuals will continue to experience even once the COVID-19 pandemic resolves. Critically, we must not be lulled into thinking that we have the luxury of time in learning from these pandemic-related findings, but rather we must act with urgency and intent to use the lessons learned from this crisis—and the new clues as to risk factors—to move toward intervention and prevention efforts that can enhance adaptive responses to the full range of potential stressors, including the likely inevitable next major natural disaster or new pandemic.

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