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Commentary

Stressed Out: Testing COVID-19's Impact on the Brain and Depression

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Stress is a robust risk factor for depression and other psychopathologies, and reward responsiveness may play a role in its connection to depression (1). Many studies exploring this possibility have measured reward responsiveness using the reward positivity (RewP), an early event-related potential reflecting the difference in neural reactivity to rewards (e.g., monetary gain) versus nonrewards (e.g., monetary loss) (2). The RewP is positive in healthy control individuals (indicating greater reactivity to reward than nonreward) and is generally blunted in individuals with or at risk for depression (2), suggesting that blunted reward responsiveness may be involved in the etiology of depression. Moreover, the RewP can be blunted by acute laboratory stressors and may be blunted in individuals with greater exposure to naturalistic stressors (3). However, it is unclear whether naturalistic stressors causally contribute to decreases in the RewP because observational designs cannot rule out several plausible, noncausal explanations for their association.

Recognizing a scientific opportunity in the devastating COVID-19 pandemic, Freeman *et al.* (4) in the current issue of *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging* used the COVID-19 pandemic as a "natural experiment" to quasi-experimentally examine the relationship between naturalistic stress exposure and reward responding. In this study, a group of 39 undergraduate students completed a task measuring the RewP both before and during the COVID-19 pandemic. This group—the pandemic group—experienced numerous pandemic-related disruptions and stressors in a range of domains (e.g., interpersonal, health) (4), which were hypothesized to contribute to decreases in reward responsiveness. As expected, the RewP (i.e., reactivity to gain minus reactivity to loss) was significantly reduced during the pandemic relative to the prepandemic baseline assessment.

However, this reduction could simply be due to the passage of time. Therefore, a key question is whether these 39 individuals' RewP decreased more than it would have if they had not experienced pandemic-related stress. Answering this question requires knowledge of how these individuals' RewP would have changed had they not experienced a pandemic (i.e., the counterfactual) (5). This is impossible to know, of course, but Freeman *et al.* (4) approximated this counterfactual by examining RewP changes in a second, highly comparable group of undergraduate students who completed the same study procedures before the onset of the COVID-19 pandemic. The two groups were discordant for exposure to pandemic-related stress between their two assessments, but matched on potentially confounding characteristics (e.g., demographics, baseline depressive symptom severity). Although less optimal than random assignment, matching the two groups on potentially confounding characteristics minimizes the impact of these characteristics on group differences and increases the likelihood that any group difference is due to pandemic-related stress.

Comparing the two groups revealed that the RewP decreased significantly more in the pandemic group than in the prepandemic group, suggesting that the pandemic group's RewP did decrease more than it would have if they had not experienced a pandemic. Follow-up analyses focusing on the pandemic group indicated that responses to gain decreased more than responses to loss, and this difference was so pronounced that responses to gain and loss no longer differed at the pandemic follow-up assessment. As the authors note, causation cannot be inferred from these data due to the lack of randomization and the possibility that decreases in the RewP were influenced by other types of pandemic-related experiences besides stressors. That said, quasi-experimental designs are perhaps the most rigorous and causally informative approach for testing causal questions when experimental manipulation is not ethical or feasible (6). The fact that associations between stress exposure and neural indices of reward responding have predominantly been studied using observational or experimental designs makes this study an especially important contribution to the literature (3). This serves as a reminder that experimental, observational, and quasi-experimental designs have complementary strengths and limitations (6). Triangulating evidence from these different methodological approaches can support stronger causal inferences and provide insight into the robustness of effects.

This study also highlights several important directions or considerations for future research. First, Freeman *et al.*'s (4) findings suggest that stress exposure may decrease reward responding, which may directly increase depression risk (Figure 1A). Decreases in reward responding did not significantly predict depressive symptoms in this study (4), but the effect was in the expected direction and the analysis may have been underpowered. More broadly, there are other potential ways in which stress and reward responding could lead to depression (1). For example, it is possible that blunted reward responding contributes to the generation of stressors, which in turn increases the risk for depression (Figure 1B). Another possibility is that reduced reward responding is a diathesis and increases one's susceptibility to depression following stressors (Figure 1C). Each of these theoretical models has received empirical support (1,3), and it is plausible that multiple models are "true." Empirical research on this topic has often tested one of these theoretical models at a time (1,3). For example, Freeman *et al.* tested one model because there were

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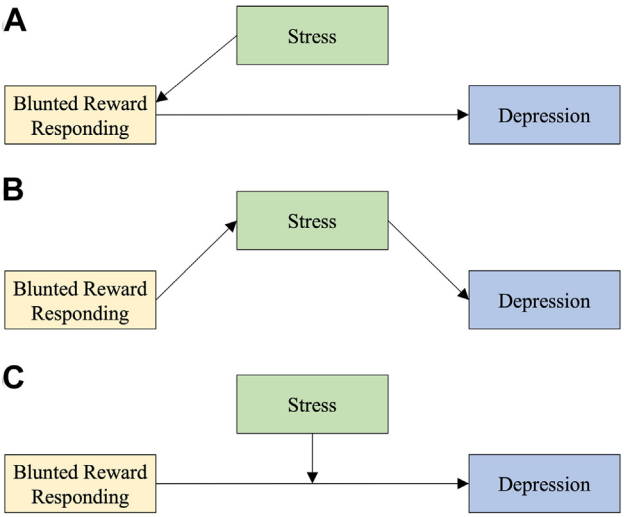

Figure 1. Theoretical models describing how stress and blunted reward responding might contribute to depression. **(A)** Reward mediation model; **(B)** stress generation model; **(C)** diathesis-stress model.

only two waves of data and the quasi-experimental design allowed for one effect (the effect of naturalistic stress on reward responding) to be tested more rigorously than others. When possible and appropriate, however, extending this approach by testing and comparing multiple theoretical models in the same data can provide insight into which theoretical model or models are most supported. This has direct implications for preventative intervention. For example, an intervention that targets and successfully increases reward responding would reduce depression risk if reward responding deficits increase depression risk either directly (Figure 1A) or by generating depressogenic stressors (Figure 1B). However, if reduced reward responding is a diathesis that leads to depression only when an individual experiences a sufficient level of stress exposure (Figure 1C), the effect of this intervention on depression risk would depend on one's level of stress exposure. For individuals who experience relatively few stressors, the intervention would have little to no effect on depression risk.

Second, this study's examination of ecologically valid naturalistic stressors was an important strength. The use of monetary rewards may be less ecologically valid, however, and is likely less representative of the most common and salient rewards in everyday life. Social rewards (e.g., acceptance) may be more ecologically valid and salient than monetary rewards and can also be delivered in standardized laboratory tasks. Of course, the actual rewards experienced in everyday life have even greater ecological validity than the social or monetary rewards one could receive in a laboratory paradigm. When and how an individual experiences and responds to rewards or stressors in everyday life can be assessed using ubiquitous personal devices (e.g., smartphones). Collecting experience sampling data can elucidate within-person fluctuations in these processes and provide insights into how these fluctuations relate to other relevant processes or outcomes (e.g., affect) over relatively short timescales (7). Depressive symptoms and risk factors (e.g., decreased reward responding, stress) are likely interrelated in complex and dynamic ways (8), and collecting a relatively large number of observations per person at an appropriate timescale affords the opportunity to better understand this complexity. Importantly, this allows for the examination of reciprocal associations, which have been reported in several longitudinal studies on stress, reward responding, and/or depressive symptoms (9). Assessing responses to naturalistic rewards at the neural level may be infeasible, but relating neural responses to rewards in the laboratory to experience sampling data collected in everyday life may be a way to gain unique insights into individuals' reward processing (10). Experience sampling data and laboratory measures data each have strengths and limitations, and each study should consider these tradeoffs in the context of their specific research question.

In sum, this study by Freeman *et al.* (4) ruled out several noncausal explanations for the effect of naturalistic stressors on decreased neural responses to reward, which in turn may contribute to increased depression risk. Future work using a variety of complementary study designs and methodologies may improve understanding of the interplay between naturalistic stress, reward processing, and depression.

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Article Information

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