Advances in stress and depression research

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Purpose of review
Stress plays a central role in the onset and course of depression. However, only a subset of people who encounter stressful life events go on to experience a depressive episode. The current review highlights recent advances in understanding when, why, and for whom the stress-depression link occurs, and we identify avenues for future research.

Recent findings
In the last 18 months, researchers have taken a more nuanced perspective on the biopsychosocial mechanisms critical to the stress–depression link. For example, examination of specific facets of emotion regulation, including emotion regulation flexibility and interpersonal emotion regulation, has been critical to understanding its role in depression. Similarly, refined investigations of social support allowed researchers to identify distinct – and occasionally opposite – outcomes depending on the context or manner in which the support was provided. Researchers also documented that the stress–depression link was enhanced by dysregulation of several stress-sensitive biological systems, such as the immune system, microbiome, endocrine system, and neuroanatomical substrates.

Summary
Recent studies highlight the importance of adopting a nuanced understanding of mechanisms and moderators that explain the stress–depression link. We also encourage continued engagement in collaborative, open science that uses multiple methods to study the full breadth of human diversity.

Keywords
affect, biopsychosocial, cognition, depression, stress

INTRODUCTION
Major depressive disorder is among the most common psychiatric disorders and is the leading cause of disability worldwide [1]. One of the most consistent findings in the depression literature is that stressful life events precipitate the onset and prolong the duration of depressive episodes [2]. Thus, a more complete understanding of depression and the etiological factors contributing to its onset, maintenance, and recurrence, necessitates consideration of the environment and the stressors it encompasses. The current review aims to discuss major advances in the stress and depression literature in the past 18 months in terms of the unique historical context this research was conducted, novel evidence for biopsychosocial pathways through which stress exposure promotes greater depression, and recent shifts in the ways clinical psychological science is conducted.

CONTEXT
The last 18 months of research on stress and depression occurred in the context of numerous major world events that significantly increased life stress exposure in the general population. For example, the coronavirus disease 2019 (COVID-19) pandemic disrupted work, education, health, finances, relationships, and recreation [3]. In addition, climate change-driven natural disasters resulted in loss of life, loss of property, and displacement. Moreover, there has been salient evidence of ongoing systemic racism and violence against people of color and other groups. Given the link between stressful life events and depression, it is unsurprising that rates of depression have increased following these events [4], particularly given that symptoms of posttraumatic stress disorder (PTSD) mediate the association.
Depression is characterized by high negative and low positive affect. As a result, it is widely conceptualized as a disorder of emotion dysregulation. In a study of adolescents, Santee and Starr [13\textsuperscript{**}] were the first to document that depression is associated with extremes of both blunted and heightened negative affective reactivity to daily hassles. Furthermore, whereas positive events offset negative affect after a stressor among individuals with depression [14], greater reductions in negative affect in response to positive events were associated with worsening depression over time [13\textsuperscript{**}]. Thus, what has previously been termed a ‘mood brightening’ effect (e.g. [15]) among depressed individuals may actually represent an ineffective overreliance on positive events to repair negative mood. Furthermore, emerging evidence suggests that emotion differentiation, the ability to identify one’s precise feelings, may represent a more adaptive buffer against stressors. Nook et al. [16], for example, recently documented that emotion differentiation attenuates the momentary association of perceived stress with depressive symptoms, possibly by facilitating emotion regulation.

Indeed, emotion regulation is posited to underlie individual differences in affective responses to stress exposure. Recent work suggests that depression is associated with habitual use of maladaptive emotion regulation strategies and infrequent use of adaptive strategies, despite evidence suggesting that individuals with depression have the ability to use adaptive strategies [17,18]. These findings underscore the utility of investigating emotion regulation strategy use as habits. Two other major shifts in the field have shaped recent emotion regulation research. The first was to continue to move beyond intraindividual conceptualizations of emotion regulation by examining how individuals regulate their emotions with the help of others, a process referred to as interpersonal emotion regulation (IER). Starr et al. [19\textsuperscript{*}] examined co-brooding (passively dwelling on feelings and problems in a dyad) and co-reflection (repetitively discussing problems to gain insight) during the pandemic. Co-brooding intensified the impact of COVID-19-related stress on depressive symptoms, whereas co-reflection buffered against the negative effects of stress exposure. Importantly, this suggests that the way in which individuals seek social support in times of stress may have opposing effects on depression. Similarly, Battaglini et al. [20\textsuperscript{*}] found that the modality through which adolescents co-ruminate had distinct downstream effects. Whereas co-rumination via text or phone had affective and/or social benefits, co-rumination via social media predicted decreases in positive affect.

The second shift that has gained momentum in emotion regulation research is investigating how flexibly emotion regulation strategies are used (i.e. emotion regulation flexibility; [21,22]). Multiple research groups have documented the value of emotion regulation flexibility, suggesting that it may promote stress resilience and attenuate risk for...
depressive symptoms (e.g. [23*,24,25**]). Wen et al. [25**], for example, tested a novel index of flexibility referred to as emotion regulation diversity, which assesses both the number of emotion regulation strategies used and the extent they are used. Interestingly, individuals with current or remitted depression evinced greater emotion regulation diversity for maladaptive strategies and less diversity for adaptive strategies, suggesting that emotion regulation diversity may play an important role in depression. Combining these two advances in the field, Battaglini et al. [23*] extended the construct of emotion regulation flexibility to examine how flexibly individuals implement interpersonal emotion regulation strategies (i.e. IER flexibility [23*]). They found that, even after accounting for the amount that IER strategies were used, IER flexibility predicted adaptive affective outcomes.

SOCIAL PATHWAYS

Given pandemic-related changes in the ways people interact, understanding social mechanisms and moderators in the link between stress and depression has become imperative. Thus, several recent studies examined stress–depression associations in the context of peer, romantic, and family relationships [26–29,30**,31]. Many of these studies focused on adolescents, which is consistent with evidence that adolescence is a window wherein harmful impacts of stress may be ameliorated via supportive caregiving [32]. Rudolph et al. [33], for example, documented the importance of parental support in buffering the effects of stress exposure (e.g. peer victimization) on adolescent depression.

However, recent findings also show that there may be situations in which social engagement catalyzes, rather than buffers, the harmful effects of stress exposure. For example, Chicoine et al. [27] found that greater support from friends in grades 6 and 8 not only failed to attenuate the impact of peer victimization but also predicted greater depressive symptoms 2 years later. Likewise, although Metts et al. [29] documented that greater support from friends predicted lower depressive symptoms, this support did not buffer the effects of early-life adversity on elevated risk for depression. Consistent with the IER findings described above [19*,20*], this may be explained, in part, by the way that individuals communicate. For example, Rodman et al. [30**] examined adolescents’ social communication as a mediator of associations between stress exposure and internalizing psychopathology. Interestingly, more frequent outgoing phone calls, but not texts, predicted greater depressive symptoms following stress exposure. Thus, it is not just whether individuals communicate but how they communicate that determines depression risk.

COGNITIVE PATHWAYS

Cognitive mechanisms have long been central to models of depression, and they continued to represent a prolific area of investigation in recent stress and depression research, with studies documenting the role of cognitive variables ranging from attribution styles and memory biases to reward responsivity. For example, Bernstein et al. [34] found that negative attributions of stressful events mediated associations of negative cognitive style with hopelessness, a common experience in depression. A growing trend was to replicate findings across laboratory and naturalistic settings. Adopting this approach, Chang and Overall [35*] found that greater recalled stress (i.e. more negative memory bias) during a conflict interaction in the laboratory and in daily life predicted greater depressive symptoms concurrently and over time. Others replicated findings across multiple samples. For instance, Trossman et al. [36] found that greater executive function-related difficulties in daily life (e.g. planning and organizing) predicted increased depressive symptoms following adverse childhood experiences across both undergraduate and community samples.

Much of this work draws from a diathesis-stress perspective, with stress exposure understood as activating cognitive vulnerability for depressive symptoms. Burani and colleagues [37,38], for example, demonstrated interactions between adolescents’ blunted neural responsivity to reward and cumulative exposure to acute stressors in predicting greater depressive symptoms. Chicoine et al. [27] also found that greater dysfunctional attitudes (i.e. related to dependency, success, and self-control) interacted with victimization in grade 6 to predict elevated depressive symptoms 2 years later.

Elucidating more fine-grained effects of specific types of stressors or facets of cognition has been an additional focus of recent work. For instance, Marchetti et al. [39*] used network analysis to examine interactions between theoretically driven components of cognitive vulnerability (i.e. dysfunctional attitudes, cognitive errors, etc.) and stress exposure in relation to depressive symptoms. In contrast to the other studies mentioned, expected interactions were nonsignificant. One possible explanation was that aspects of cognitive vulnerability might be stressor-specific, meaning that not all stressors activate cognitive mechanisms implicated in depression. Though other explanations are also possible, such research supports the complexity of pathways...
among stress, cognition, and depression and the need for more nuanced investigations of these associations.

**BIOLOGICAL PATHWAYS**

Recent studies have extended our understanding of the biological bases of the stress–depression link by investigating mechanisms that contribute to changes in key biological systems. Bolstered by technological advances that have increased both capacity and feasibility in this area, recent research has focused particularly on dysregulations of stress-sensitive biological systems implicated in the pathogenesis of depression. These include dysregulation within the immune system, microbiome, endocrine system, and neuroanatomical substrates.

Meta-analytic evidence has consistently documented associations of several inflammatory markers [e.g., C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor alpha (TNF-α)] with depression [40]. However, it has historically been unclear whether these are stable markers that are present outside of depressive episodes, which is key to delineating the role of inflammation as a precipitating factor of depressive illness. Several research groups have worked recently to fill this gap in the literature. Zainal and Newman [41], for example, offered an empirical test of the cytokine theory of depression [42,43] and documented that increased levels of CRP, IL-6, and fibrinogen predict changes in depression diagnosis 9 years later (as evidenced via depressive episode development or relapse), particularly among those at risk for depression (e.g., women, and those with low income or higher childhood trauma).

The microbiome also represents an exciting realm for exploration within the stress–depression literature. Emerging evidence supports the role of the gut microbiome in mood regulation and highlights the role of stress in this association [44]. Recent investigations using animal models have documented that chronic stress induces disturbances in the microbiota and that antibiotic treatment reverses stress-related depressive behaviors [45]. Translational work in humans further supports the role of the microbiome as a mechanism through which stress is related to depression. For example, Coley et al. [46] found that early-life stress was associated with alterations in the brain–gut axis, which in turn predict elevated levels of perceived stress and depression during adulthood. While this work is preliminary, it highlights a promising emerging area of investigation.

Finally, advances in our understanding of the neural correlates of depression highlight the role of stress in the pathophysiology of the illness. Of particular note are findings from the ENIGMA-MDD consortium, which pools data from multiple samples worldwide. Findings from the consortium indicate structural differences between those with and without depression in brain regions that are sensitive to the effects of stress [47]. Moreover, individuals with depression show advanced brain-related aging compared with nondepressed participants [48]. Findings from the consortium also provide support for a diathesis-stress model. Whittle et al. [49], for example, found that cortical thickness across multiple neural regions interacted with educational attainment to predict depression.

**CONCLUSIONS AND FUTURE DIRECTIONS**

There have been numerous advances in stress and depression research in the past 18 months. Increasing evidence documents that the connection between stress exposure and depression is influenced by affective, social, cognitive, and biological factors and their association with one another [50]. One theme that emerged across multiple studies is the importance of developing a nuanced, rather than a global, understanding of mechanisms and moderators that explain the stress–depression link. For example, we have been able to better understand the role of emotion regulation in depression by considering nuanced conceptualization of emotion regulation flexibility, interpersonal emotion regulation, and the communication modality in which emotion regulation occurs [19*,20*,23*,25**]. Similarly, nuanced investigations of social support allowed researchers to identify distinct, and occasionally opposite, outcomes depending on the context or manner in which the support was provided [25**]. Even putatively established protective factors were not universally helpful, with findings indicating that we must consider characteristics of the individual or the stressor [27,29]. This possibility is consistent with evidence that factors such as stressor type, duration, and severity influence risk for depression, and that different stressor characteristics may confer risk for different people [2,51]. The need to examine both risk and resilience factors was also apparent. Indeed, across subfields, there was an increased focus on documenting factors promoting wellbeing in the face of stress, such as co-reflection, emotion regulation flexibility, social support, and reparative environments [19*,24,27,52].

On an even broader scale, there has been an increased focus on open, collaborative, and representative science, which constitutes a critical direction for future research. Researchers are increasingly preregistering their hypotheses and analytic plans.
and sharing their measures, statistical code, and data to promote the transparency, reproducibility, and replicability. In recent months, the value of collaborative science was highlighted in the context of multisite and multinational studies, which provided evidence of global increases in stress and depression during the COVID-19 pandemic [33]. A significant benefit of collaborative science is that it enables rich interdisciplinary work. Interdisciplinary teams have leveraged members’ varied expertise to conduct multimethod studies that incorporate biological, cognitive, and self-report variables [54*]. Doing so allows researchers to examine connections between factors, thereby informing integrative models of depression in ways that reflect the complexity of the disorder. Many of these studies have capitalized on technological advances to move beyond the laboratory and into individuals’ everyday life, thereby investigating naturalistic and ecologically valid stressors (e.g. [35*]). Studies are also using varying time scales to model associative trajectories between stress and depression on a moment-to-moment, day-to-day, and year-to-year scale (e.g. [30**,34]).

Finally, the field has increasingly recognized the importance of considering the full spectrum of human diversity, which has been neglected over much of its history. Indeed, a growing literature investigates the impact of stressors related to gender diversity and marginalization on depression (e.g. [55]). This increased emphasis on diversity also includes cultural and racial diversity, with recent work providing a much needed spotlight on these constructs [56,57**]. One approach that will inevitably help acknowledge the spectrum of human diversity is community-based participatory research, in which researchers and community stakeholders collaborate as equal partners in the research process.

As the global pandemic, climate, and geopolitical context continue to shift and change, a continued focus on these themes is critical for us to continue the progress of the last 18 months. By engaging in collaborative, open science that uses multiple methods to study the full breadth of human diversity, challenging foundational assumptions, and examining both risk and resilience, we move towards a more fulsome understanding of the link between stress and depression.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:
• of special interest
• • of outstanding interest


This study was the first to document that both blunted and heightened negative affectivity to hassles are associated with elevated depressive symptoms in adolescents. This nuanced association between depressive symptoms and affective reactivity explain contradictory findings in the literature and point to the need to integrate models that posit that depression is linked with diminished (emotional context insensitivity) or with heighted (negative-potentiation hypothesis) affective reactivity.


This study demonstrates that co-brooding and co-reflection have opposing effects on depression following COVID-19-related stress. This indicates that the way in which individuals elicit others’ support via different forms of interpersonal emotion regulation have unique impacts on depression.


The authors were the first to document that the domains in which individuals co-ruminate influence affect and relationship closeness. Co-rumination through text and over the phone had affective and/or social benefits, whereas co-rumination through social media predicted diminished positive affect.
Mood and anxiety disorders


39. C-reactive protein, fibrinogen, and interleukin-6 levels predicted the onset or recurrence of episodes, particularly in younger adults, women, those with low income, and those with high childhood trauma.


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