Biological Responses to Acute Stress and Suicide: a Review and Opportunities for Methodological Innovation

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Abstract
Purpose of Review While rates of other medical illnesses have declined over the past several decades, rates of suicide have increased, particularly among adolescents. Prior research on biological underpinnings of suicide risk has remained limited. In this review, we describe a recent model conceptualizing suicide as a failure of biological responses to acute stress. According to this model, youth who fail to mount an adaptive stress response following exposure to a stressor are at acute risk for suicide.

Recent Findings Although much more research is needed, early evidence suggests that abnormal biological responses to acute stress, such as altered autonomic nervous system activity and altered hypothalamic-pituitary-adrenal axis function, may underlie risk for suicide, particularly during the transition to adolescence.

Summary Overall, initial evidence supports a link between biological responses to acute stress and suicide risk. However, future work that incorporates makers of other biological and environmental systems will sharpen our understanding of who is at suicide risk and when this risk is highest.

Keywords Suicidal ideation · Suicidal behavior · Stress and suicide · Within-person models of suicide

Introduction
Suicide is a leading cause of death worldwide [1, 2]. Over the past several decades in the USA, rates of most medical illnesses have declined while rates of suicide death have risen [1]. Despite many years of research, our ability to prospectively predict suicide remains critically limited [3••]. Past research has provided a wealth of knowledge regarding correlates and risk factors for suicide. However, one underexplored area is the role of biological responses to acute stressors and resulting risk for suicide. This review discusses a recent conceptual model that aims to improve our understanding of the behavioral and biological processes that occur in the moments of a suicidal crisis.

Self-injurious thoughts and behaviors encompass a wide range of behaviors used by individuals to deliberately inflict non-fatal or fatal bodily harm. Constructs include nonsuicidal self-injury (NSSI; see Table 1 for abbreviations used throughout manuscript), defined as self-inflicted tissue damage without suicidal intent, as well as suicidal ideation, suicidal plans, suicidal gestures, and a range of suicidal behaviors (i.e., interrupted attempts, aborted attempts, suicide attempts, and death by suicide) [4, 5]. Although NSSI is both a correlate and risk factor for suicidal ideation and behavior, prior research demonstrates that NSSI is distinct from suicidal ideation and behavior with unique predictors and developmental course. Thus, we refer readers to excellent reviews on NSSI (see [6–8]). In the present manuscript, we focus primarily on suicidal ideation and behavior.

Suicidal ideation and behaviors have a clear developmental onset. Beginning around the pubertal transition, rates of suicidal ideation and behavior increase precipitously throughout adolescence until rates stabilize in emerging adulthood [9]. This sharp increase occurs across every country in the world [10]. The nearly universal increase in suicidal ideation and behavior during adolescence suggests some core, underlying biological vulnerability that has yet to be identified. Yet, extant theories of suicide neither take a lifespan development...
perspectives nor acknowledge underlying biological vulnerabilities that may elucidate risk [11]. We believe that to understand risk for suicide, it is critical to adopt a lifespan developmental perspective. Specifically, complex interactions between social and biological factors throughout developmental likely shape any given individual’s risk for suicide. Adolescence, in particular, represents an ideal example of the interaction between biological systems and suicide risk [11]. As such, we primarily focus on adolescence throughout this review, noting where studies draw from or may apply to adults as appropriate.

In this manuscript, we briefly discuss prior theories of suicide and review a recent conceptual model of suicide and biological responses to stressors offered by Miller and Prinstein [11]. We encourage readers to consult the longer, more expansive review by Miller and Prinstein for a comprehensive overview of biological responses to stressors and adolescent suicide. Next, we provide a succinct overview of extant available research on core biological systems that respond to stressors and suicidal ideation and behavior. Then, the remainder of the manuscript discusses opportunities for methodological innovation that will better elucidate the complex interactions between biology and suicide risk.

Prior Theories of Suicide

A brief review of prior theories of suicide helps contextualize the current review’s focus on suicide and biological responses to stressors. Though they differ in important ways, theories of suicide generally agree on major components of suicide risk. First, theories agree that interpersonal distress is a central component to an individual’s decision to engage in lethal self-harm. For example, classic theories (e.g., Durkheim [12], Baumeister [13], Shneidman [14]) emphasize that social isolation, distress about one’s social standing, and resulting mental pain lead to suicidal ideation and behavior. More recent theories (e.g., Interpersonal Psychological Theory [15, 16]; 3-Step Theory [17]; Integrated Motivational Volitional Theory [18]) highlight the central role that negative interpersonal states play in suicidal ideation and behavior. Second, theories suggest that suicidal ideation and behaviors arise from subjective affective distress, sometimes cascading into cognitive inflexibility. Early theories note that rigid, distorted thinking leads individuals to view suicide as a reasonable option for dealing with emotional distress [13, 19–22]. More recent work suggests that dysfunctional cognitions related to stressors and self-worth may underlie risk for suicidal behavior [15, 17]. Third, theories suggest that stressor exposure and resulting dysregulation lead individuals to engage in behaviors that increase risk for suicide. Indeed, cognitive and dialectical theories suggest that as individuals experience stressors, they may engage in behaviors, such as substance use and self-harm, in an attempt to self-regulate, but these behaviors may actually make suicidal behavior more likely [21, 23, 24]. While other areas of research widely acknowledge that stress exposure results in a cascade of biological responses aimed at mounting effective defenses [25], theories of suicide have rarely incorporated these biological underpinnings, with two notable exceptions. Linehan’s theory of suicidal behavior suggests that individuals at risk for self-harm experience abnormal biological signaling following stressor exposure. Joiner’s IPT theory suggests that the ability to enact lethal self-harm is acquired over the lifespan, with physically painful or dangerous situations altering the body’s biological response to self-injury [16]. We argue that the body’s responses to environmental stressors are likely key for understanding acute risk for suicidal ideation and behavior.

Stress Response Systems

Recently, Miller and Prinstein [11] suggested that adolescent suicide may result from failures in biological responses to acute stressors. According to this theory, adolescents at risk for suicide experience maladaptive biological responses to stressors that increase proximal risk for suicidal ideation and behavior. In their review, Miller and Prinstein describe two key biological systems that are responsive to stressors and have been implicated in suicidal ideation and behavior, including the autonomic nervous system (ANS) and the hypothalamic-pituitary-adrenal axis. In brief, the fast-acting ANS triggers the “fight-or-flight” stress response, which prepares the body to flexibly adapt to a stressor. The parasympathetic nervous system (PNS) modulates the “flight-or-flight” response via the vagus nerve [26]. The control of the vagus nerve on the ANS is indexed via respiratory sinus arrhythmia (RSA), the ebbing and flowing of heart rate across the breath cycle [26, 27]. During exhalation, the PNS inhibits or acts as a “brake” on the sympathetic nervous system, while inhalation results in decreased inhibition of the sympathetic response. In this way, the PNS facilitates alert engagement in the environment [26, 28]. In response to stressors, PNS withdrawal (indexed via RSA decreases or suppression) occurs instantaneously. Dynamic RSA responses across contexts are essential for adaptive physiological responses and associated psychological adjustment [29]. Thus, the ANS and PNS are fast-acting systems that ready the body’s response to stressors.

In response to a stressor, the slower acting HPA axis activates the paraventricular nucleus (PVN), which stimulates the release of corticotropin-releasing hormone. This in turn causes the pituitary gland to release adrenocorticotropic hormone (ACTH). Then, ACTH stimulates the adrenal glands to synthesize and release glucocorticoids, which are the end point of the HPA axis. Glucocorticoids (cortisol in humans) have been implicated in many adaptive responses to stress, including enhanced memory [30] and regulation of inflammatory immune signaling [31]. The HPA axis, then, further prepares the body’s responses to acute stressors in the environment.
Biological responses to stressors are triggered, regulated, and terminated via neural mechanisms. As above, the vagus nerve modulates the ANS and transmits afferent signals to subcortical areas of the brain (e.g., amygdala) via the nucleus tractus solitarius [32]. Glucocorticoids signal the HPA axis to shut off via targeted brain structures, including the PVN, hippocampus, amygdala, and prefrontal cortex regions [33, 34]. Thus, stress responses are intimately tied to function within subcortical and cortical regions of the brain.

Although not traditionally conceptualized as a biological system directly tied to stress responses (and not originally included in the Miller and Prinstein review), the hypothalamic-pituitary-gonadal (HPG) axis has emerged as a regulator of both stress responses and suicidal ideation and behavior, particularly in females. Adolescent girls experience their first menstrual cycle (i.e., menarche) at the end of puberty, which introduces regular monthly fluctuations in the ovarian hormones estradiol (E2) and progesterone (P4). Ovarian hormones are highly conserved signaling molecules that regulate the ANS, the HPA axis, and brain structure and function. In adult experiments, ovarian suppression reduces corticotropin-releasing hormone–induced output of ACTH and cortisol, whereas addback of P4 (but not E2) increases ACTH and cortisol output [35]. Our recent meta-analysis of 37 studies also suggests that P4 reduces PNS function; the final week of the menstrual cycle, characterized by exposure (or recent exposure) to high P4, is associated with lower cardiac vagal activity (e.g., RSA) relative to the menstrual and mid-follicular (low P4) phases [36]. Finally, there is a body of evidence demonstrating a variety of ovarian hormone effects on brain structure and function (reviewed in [37]), including evidence for luteal blunting of the amygdala and medial prefrontal cortex responses to stress [38], and perimenstrual increases in amygdala gray matter [39], both of which correlate with greater stress-induced negative affect. In sum, ovarian hormones regulate key mediators of stress response, including the HPA axis, the ANS, and the stress-responsive circuits in the brain.

Biological systems that respond to stressors follow a developmental pattern. Starting at the transition to adolescence, both animals and humans undergo pronounced changes in biological responses to acute stressors [40]. These developmental adaptations result in a period of protracted increased reactivity to stressors with a slower return to baseline [40–44]. Interestingly, this developmental shift coincides with the precipitous increase in psychopathology broadly [45] and suicidal thoughts and behaviors specifically [9, 11]. In addition to these biological changes, adolescence is characterized by rapid social reorganization and increased exposure to interpersonal stressors [46]. Together, typical adolescent development is characterized by increased sensitivity and responsiveness to environmental stressors. Accumulating evidence suggests that atypical biological responses to acute stressors have implications for understanding emotion regulation [47, 48••, 49] and both internalizing and externalizing problems [31, 50–52]. Further, a vast literature demonstrates that experiences during childhood and adolescence have far reaching effects on stress response in adulthood [53]. Note also that some early experiences that have been implicated in stress response functioning in adults, such as child maltreatment, are also consistently implicated as distal predictors of suicidal ideation and behavior [54].

**Biological Markers of Stress Systems and Suicide**

According to the conceptual model put forth by Miller and Prinstein [11], suicidal crises in youth may be precipitated by failures in biological responses to acute stressors. As depicted in Fig. 1, suicidal ideation and behaviors may result from altered biological responses to acute stressors. As can be seen in the figure, each of the biological systems does not operate in isolation. The precise directionality among the systems is not currently known; however, this model suggests that failures within one or several of these stress systems may contribute risk for suicidal ideation and behavior. Below, we briefly review some of the main findings from extant research linking markers of the ANS and the HPA axis with suicidal ideation and behavior, which are reviewed in detail in Miller and Prinstein [11]. We also comment briefly on work examining neural markers of suicide risk and more recent research on ovarian hormone cycling and suicide risk. Importantly, the majority of work examining biological markers of stress

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**Fig. 1** Conceptual model depicting the links between early distal risk factors, altered biological responses to acute stressors, and risk for suicidal ideation and behavior. We depict bidirectional relationships between biological systems because the precise interrelationships among these systems, especially over time, are still unknown. HPA, hypothalamic-pituitary-adrenal axis; HPG, hypothalamic-pituitary-gonadal axis; ANS, autonomic nervous system.
response systems and suicide has been conducted in adult samples. We comment specifically below when findings are in adult or adolescent samples. Most of this work is cross-sectional in nature, with few longitudinal studies.

ANS Overarching findings suggest that lower resting RSA or excessive RSA withdrawal may be linked with emotion dysregulation and suicidal ideation and behavior. However, the precise associations remain unclear. In general, concurrent studies support an association between a history of suicidal behavior and lower resting and excessive RSA withdrawal among adolescent girls [55] as well as a link between history of suicidal ideation and lack of flexible RSA responding among youth [56]. A recent cross-sectional study found that adolescents with either suicidal ideation or suicide attempt histories (compared with depressed and non-depressed controls) did not evidence flexible RSA responses to a lab-based frustration task [57]. Longitudinal work is more equivocal with some studies finding a prospective link between altered resting and stress-related withdrawal RSA and suicidal ideation among adolescents [58] while others do not find this association among adolescents [59]. More longitudinal research is needed to understand the precise link between RSA and prospective suicidal ideation and behavior. While mixed, preliminary evidence points to RSA as a promising marker of acute risk for suicide.

HPA Axis Studies have linked markers of the HPA axis with suicidal ideation and behavior, including resting or baseline cortisol, chronic cortisol output measured via hair samples, and cortisol reactivity via repeated salivary sampling during an experimentally administered stressor. Elevated baseline cortisol has been linked with frequency of suicidal behavior in adults [60], but more recent work shows lower chronic cortisol levels among individuals (mixed samples of adults and adolescents) with suicidal behavior compared with those with only suicidal ideation or healthy controls [61, 62]. Cross-sectional studies have found that adults with a history of suicide attempts show blunted cortisol reactivity during a social stressor task (Trier Social Stressor Task) [62, 63]. Longitudinal work from our group has demonstrated that exaggerated cortisol responses during the Trier Social Stressor Task (TSST) predict suicidal ideation severity across 3 months [58] among adolescent girls, while blunted cortisol responses predict suicidal behaviors during times of increased stress across 18 months [64] among adolescent girls.

Neural Markers Though still in its infancy, emerging findings from neuroscience suggest a link between suicide risk and altered neural structure and function in regions implicated in biological responses to acute stressors in both adolescents and adults. Biological responses to acute stressors are modulated within neural circuits within the brain. Subcortical brain structures, such as the amygdala and hippocampus, monitor the environment for threats or reward. In turn, these subcortical structures are regulated by prefrontal brain structures. Thus, altered structure and function in these areas may signal risk for maladaptive responses to acute stressors and subsequent suicidal ideation and behavior. Initial work by Johnston and colleagues [65] demonstrated that youth with histories of suicidal behavior (vs. controls) had reduced gray matter volume in the hippocampus and cerebellum and decreased functional connectivity between the amygdala and left ventral and right rostral prefrontal cortex when viewing affective faces. Quevedo et al. [66] found that youth with histories of suicidal ideation and behavior show reduced activation in the hippocampus and amygdala when viewing happy faces, suggesting altered processing of environmental stimuli. An emerging line of work also supports altered neural activation [47, 66, 67, 68] and network connectivity [69–72] in prefrontal cortex regions among adolescents with suicidal ideation and behavior histories. One study found altered dorsolateral prefrontal cortex activation during attempts to effortlessly regulate affective responses to negative stimuli among youth with suicidal ideation histories (vs. no suicidal ideation) [47]. Similarly, altered connectivity within the salience network, which has been implicated in reactivity to stressors and includes the amygdala and prefrontal cortex regions, has been associated with suicidal ideation among adolescents [69, 70, 73]. In adult samples, similar findings have emerged suggesting decreased functional connectivity between prefrontal control regions and subcortical stress reactive regions in individuals with suicidal ideation [74–76]. Though more research is necessary, emerging findings suggest altered activation and connectivity patterns between prefrontal and subcortical brain regions which may result in increased reactivity to environmental stressors and decreased capacity to resist the urge to engage in lethal self-harm.

HPG Axis Among adult females, ovarian hormone fluctuations across the menstrual cycle have been linked to cyclically occurring windows of increased suicide risk. In particular, the perimenstrual phase of the cycle—the week surrounding menstrual onset—has been repeatedly linked with increased likelihood of hospital admission for suicidal behavior and suicide death among adults [77, 78]. Additionally, an experimental study of hormone stabilization (vs. natural perimenstrual hormone withdrawal) conducted in our laboratory has recently provided support for a causal role of ovarian hormone withdrawal in suicidal ideation severity among adults [79]. We hypothesize that these cyclical changes in suicidal processes are attributable, in part, to the effects of cyclical hormone changes on biological stress response mediators (reviewed above). Additional pathways likely include direct effects of hormone changes on mood and the perception or generation of social stressors in daily life, particularly among adult...
females who are especially sensitive to hormonal changes [80]. Unfortunately, there are no published repeated measures studies examining the association between the menstrual cycle and suicide risk in adolescence—a time of substantial change in stress physiology and recalibration of biological systems.

In sum, initial research supports a link between biological responses to acute stressors and suicide risk. Yet, these systems are often studied in isolation, and more longitudinal research is necessary to gain a clearer understanding of the mechanisms linking biological stress responses with suicide risk.

**Opportunities for Methodological Innovation**

Suicide is a complex problem that likely results from transactions among numerous biological and psychological processes. To date, most prior suicide research, including our own, has attempted to study risk for suicide using a handful of risk factors [3••]. This is understandable, given the considerable challenges inherent in researching a behavior with such a low base rate. Nevertheless, as we and others have argued, suicide risk is best understood as resulting from a culmination of multiple factors that may vary from person to person and over time [3••, 11]. In this section, we describe two key opportunities for methodological innovation that will sharpen our understanding of the relationship between biological responses to acute stressors and suicide.

**Opportunity 1: Capturing between- and within-person variability to understand acute suicide risk**

We argue that suicide risk is best captured by careful assessment of risk factors from both between- and within-person perspectives.

To illustrate what we mean by between- and within-person suicide risk, we briefly present two common clinical examples of suicide risk that we see in our research studies and practice (see Fig. 2, panel a). Teen A is a 14-year-old girl with a history of significant childhood adversity exposure and chronic life stress. Over the course of a 6-month observation period, Teen A reports substantial environmental stressors and subjective feelings of stress on a weekly basis. However, 1 week, she reports more stress than is typical for her citing a recent romantic breakup. Teen B is a 13-year-old girl with an unremarkable developmental history who nonetheless experiences chronic social anxiety. Over the course of a 6-month observation period, Teen B reports few environmental stressors but moderate subjective feelings of stress on a weekly basis. However, 1 week, she presents much more distressed than usual and reports a major fight with her best friend. Who is at greater risk for suicide?

Traditional theories and research studies would likely flag Teen A as high risk for suicidal ideation and behavior due to her higher overall exposure to stressors and higher reports of subjective distress. Indeed, she has a higher mean level of stress than Teen B, and more distal risk factors for suicide. This approach to understanding risk is consistent with the majority of prior research wherein greater between-person (mean) levels of a given risk factor are associated with greater risk for suicidal ideation and behavior. However, the model put forth by Miller and Prinstein [11] suggests that both teens may be at risk for suicidal ideation and behavior if they share similar altered biological responses to acute stressors (as a trait). Additionally, a key hypothesis from the above examples is that the week where each teen reports higher-than-usual stress may also signal enhanced windows of risk for suicide—that is, when each girl exceeds her own stress threshold, she may be at acute suicide risk. Better capturing and modeling this within-person variability is critical to improve our prediction of when any given individual is at risk for suicide.

We have published a series of initial studies that directly test this stress threshold model with regard to predicting suicidal ideation, suicidal behavior, and NSSI. In a multi-wave study of 220 adolescent girls, we found modest between-person associations between interpersonal stress and suicidal
ideation and behavior across an 18-month period. However, our ability to prospectively predict suicidal ideation and behavior markedly improved when we examined within-person fluctuations in stress within each 3-month follow-up period. Indeed, we found that girls were more likely to report suicidal ideation during times when they experienced higher-than-usual (compared with their own average) interpersonal stressors. Findings also suggested that periods of higher-than-usual stress signal times of enhanced risk for suicidal behavior particularly among girls who reported a distal history of sexual or physical abuse [81]. Critically, this interaction joins a between-person factor (trauma) and a within-person factor (time-varying stress) to improve risk prediction.

We recently extended these initial findings in several important ways. First, within the same sample, we found a social-biological transactive effect consistent with the biological stress system and suicide model presented above: suicidal behavior was most likely among girls with a blunted (hyporeactive cortisol response) to a social speech task, and this between-person factor again predicted a stronger relationship between higher-than-usual peer stress and suicidal behaviors (within-person) [64]. Second, we recently extended this model to the related behavior of NSSI. In two separate samples, we found that higher between-person stress was not associated with risk for NSSI. Rather, periods of higher-than-usual (within-person) stress were associated with increased NSSI risk. Finally, ongoing work in our laboratory has revealed the role of the menstrual cycle in predicting within-person risk for suicide, and the role of between-person differences in hormone sensitivity in long-term suicide risk.

Opportunity 2: Combining assessments across multiple units of biobehavioral analysis

Studies that measure stressors and multiple stress-responsive systems across different units of analysis will sharpen our understanding of the links between stressors and suicide, both between-person and within-person over time.

The dynamic systems that ultimately lead to suicide can be measured at various biological and behavioral levels, as exemplified in the National Institutes of Mental Health (NIMH) Research Domain Criteria (RDoC) system. Recent narrative [82] and meta-analytic [83] reviews of the literature highlight the diverse ways in which stressors and stress responses have been assessed across RDoC domains and linked to suicide outcomes. However, few studies have examined multiple units of analysis at once, and almost none has examined how these dynamic systems interact over time to produce within-person, acute risk for suicide (see Opportunity 1). Of note, greater integration of suicide risk processes at multiple levels of analysis is a current priority of the National Institute of Mental Health as well as the NIMH co-sponsored Prioritized Research Agenda for Suicide Prevention [84]. Ideally, combining different systems (i.e., RDoC Domains or subconstructs) across different units of analysis (e.g., genomic, molecular, physiological, and behavioral) will increase precision in our prediction of who (between-person) is at risk for suicide and when (i.e., what time-varying factors help to predict when) someone is at risk for suicide following exposure to acute stressors.

Extending our illustration above, we elaborate on our two clinical examples (Fig. 2, panel b) by outlining two hypothetical risk-generating scenarios in which dual fluctuations in stressor exposure and underlying vulnerability of biological stress response systems interact to produce windows of acute suicide risk (pictured in gray in Fig. 2, panel b). Of note, each of our hypothetical patients/participants is at elevated between-person risk (due to trauma in the case of Teen A, due to social anxiety disorder in the case of Teen B). Cross-sectionally, these two individuals can be compared on biological responses to acute stressors as reviewed above to determine which aspects of trait-like stress responding may be altered in those with a history of suicidal ideation or behavior. This would provide some insight into who is at greater risk. However, when multiple stress-responsive systems are measured along with suicide risk at various units of analysis over time, we can start to gain an even clearer picture of how systems interact over time to produce episodes of acute risk for each girl. This would provide sharper precision in predicting when someone is at increased suicide risk. Of course, these approaches are most powerful when combined with fine-grained assessments of behavior in real time, consistent with recent research interest in EMA and suicide risk [85, 86].

Future research on biological stress systems and suicide will benefit from taking an RDoC informed approach by gathering data across multiple units of analysis. Several existing programs of research provide exciting glimpses into the power of such careful within- and between-person analysis. In our labs, we have examined the main and interactive effects of distal risk factors for suicide (e.g., trauma exposure, baseline cortisol reactivity to a social stressor) as well as time-varying, within-person factors, such as prospective assessment of interpersonal stress, on prospective risk for suicide in adolescent girls [58, 64, 81, 87, 88]. A recent prospective and experimental study in our lab has also examined the effects of prospectively assessed cyclical hormone fluctuations on suicidal ideation severity, finding that monthly perimenstrual hormone withdrawal leads to week-long windows of elevated suicide risk in naturally cycling adult females [79]. A handful of research studies have also begun to examine neural markers of risk for suicidal ideation and behavior in adolescents, including a focus on resting-state functional connectivity [65, 70, 73] and functional activation differences in processes hypothesized to underlie suicide risk [47, 68, 69]. Finally, a series of studies are currently underway combining mobile monitoring technology (passive monitoring from smartphones and...
wearable technology) to predict real-time risk for suicidal thoughts and behavior and related processes. As research continues to evolve, future studies that combine methodologies, such as fMRI, behavioral assessments, markers of stress responses, and mobile monitoring, are necessary to gain further clarity into between- and within-person differences in acute risk for suicide.

Conclusions

Here, we have articulated the crucial role of biological responses to acute stressors and suicide risk. In our hypothetical examples in the present manuscript, we have outlined 2–3 pathways to suicide through biological responses to acute stressors that might function differently between- and within-person. In reality, there likely are numerous risk pathways that lead to suicide. By narrowing our focus to a single pathway (e.g., trauma leading to blunted cortisol responding resulting in subsequent stress-related suicidal behavior), we may miss other high-risk profiles, such as individuals with attention and hyperactivity problems and chronic self-injury. As reviewed above, theories of suicide share common elements. Rather than viewing them as in competition with one another, we should consider the possibility that they explain different risk pathways that unfold in different people or in different points in time. The public health crisis of suicide necessitates innovative research strategies that combine knowledge across multiple disciplines, theories, and methodologies.

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Compliance with Ethical Standards

Conflict of Interest Tory Eisenlohr-Moul reports grants from the National Institute of Mental Health during the conduct of the study. Adam Bryant Miller declares no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance


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biological responses to acute stressors. Data in support of this model are reviewed in detail, and this is a more expansive version of the first portion of this review paper.


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