Adolescent Suicide as a Failure of Acute Stress Response Systems

Adam Bryant Miller
adam.miller@unc.edu

Mitchell J. Prinstein
mitch_prinstein@unc.edu

University of North Carolina at Chapel Hill

Shortened Running Title: Adolescent Suicide and Stress Response

Corresponding author: Adam Bryant Miller, PhD. adam.miller@unc.edu, UNC Psychology and Neuroscience, Davie Hall, Campus Box B 3270, Chapel Hill, NC 27599-3270

Acknowledgements: Preparation of this manuscript was supported by grants from the National Institute of Mental Health (R01MH107479, F32MH108238, & K01MH116325).

Please use the following citation:


This is a post-print draft of the manuscript, which has been accepted for publication in the Annual Review of Clinical Psychology. Please see the publisher’s website for the final corrected manuscript: https://www.annualreviews.org/loi/clinpsy
Abstract

Suicide currently is the second leading cause of death worldwide for adolescents. Despite decades of research on correlates and risk factors for adolescent suicide, we know very little about why suicidal ideation and behavior frequently emerge in adolescence and how to predict and ultimately prevent suicidal behavior among youth. In this review, we first discuss current knowledge regarding correlates, risk factors, and theories of suicide. We then review why adolescence is a period of unique vulnerability given changing biology and social network reorganization. Next, we present a conceptual model with which to interpret emerging findings in adolescent suicide research. We suggest that a promising area for future research is to examine adolescent suicide as a failure of acute biological stress response systems in the proximal moments of a suicidal crisis. After reviewing initial evidence for this conceptualization, we review future directions for studies on adolescent suicide.

Key Words: suicidal thoughts, stress-response, suicidal behavior, acute suicidal crisis
Table of Contents

Introduction and Background
  Scope of Review
Correlates, Risk Factors, and Theories of Suicide
  Current Knowledge About Correlates and Risk Factors
  Theories of Suicide
Adolescence: A Critical Time of Vulnerability to Suicide
  The Adolescent Transition
  Typical Acute Biological Stress Responses
  Associations Among Biological Markers of Stress Response and Suicide
  Markers of Central Response Systems
    Autonomic Nervous System
    Hypothalamic-Pituitary-Adrenal Axis
  Peripheral Stress Response Systems and Functional Genomics
    Cytokines
    Other Epigenetic Markers
  Neural Markers
Synthesis and Future Directions
  Stress Threshold
  Suicide Propinquity
Conclusions
Terms/Definitions list:

- Suicidal ideation – includes consideration of, or desire for death that can range from passive (e.g., “I would be better off dead.”) to active (e.g., “I plan to kill myself.”).
- Suicide attempt – refers to a deliberate action to end one’s life
- Suicidal behavior – sometimes used to encompass both actual and interrupted suicide attempts.
- Suicide death – results from fatal, deliberate self-harm frequently determined by medical examiner or coroner

Acronyms List:

- ANS: Autonomic Nervous System
- PNS: Parasympathetic Nervous System
- SNS: Sympathetic Nervous System
- RSA: Respiratory-Sinus Arrhythmia
- HPA: Hypothalamic-Pituitary-Adrenal
- PFC: Prefrontal Cortex
Suicide is the second leading cause of death worldwide among individuals between 10 and 24 years of age (Curtin et al. 2016; Mokdad et al. 2016) representing an alarming public health crisis. Suicidal ideation and behaviors are even more common than death by suicide. Prevalence rates range from 19.8% to 24% for suicidal ideation and from 3.1% to 8.8% for suicide attempts among youth (Nock et al. 2008). Suicidal ideation and behaviors are the most common mental health emergencies among adolescents (King et al. 2009). Despite these disturbing statistics, our ability to accurately predict suicidal ideation and behavior as well as death by suicide remains remarkably limited (Franklin et al. 2017). In this review, we offer a synthesis and framework for understanding the proximal processes involved in adolescent suicidal ideation and behavior. Specifically, we suggest that failures in biological stress responses may underlie acute suicidal crises in youth. We first review prior research on adolescent suicide before offering an assessment of contemporary research and future directions.

**Scope of Review**

Self-injurious thoughts and behaviors include a wide range of actions used by individuals to deliberately inflict non-fatal or fatal bodily harm. Constructs include nonsuicidal self-injury (NSSI), 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, suicidal attempts ranging in lethality and subsequent medical attention, and death by suicide) (O’Carroll et al. 1996; Silverman et al. 2007). Notably, the distinction between these constructs is sometimes unclear, particularly among youth who may not be able to articulate their intent to die before considering or engaging in suicidal behavior (Hawton et al. 2012; Prinstein 2008). Nevertheless, prior research clearly has revealed NSSI as both a correlate and risk factor for suicidal ideation and behavior; yet, the predictors and
developmental course of NSSI differs than that of suicidal ideation and behaviors (see reviews by Fox et al. 2015; Liu et al. 2017). Thus, we elected to focus this review specifically on suicidal self-injurious thoughts and behavior and do not review literature on NSSI.

Moreover, it should be noted that far more research has examined suicide ideation and suicidal attempts than other suicidal constructs (i.e., plans, gestures, interrupted or aborted attempts, and death by suicide), particularly among youth. Thus, readers are cautioned against generalizing findings across suicide constructs, or assuming equivalence in the theories and predictors for various types of suicidal ideation and behaviors. For simplicity in prose, we use the terms suicidal ideation and suicidal behavior herein. We note where findings have been studied in relation to suicide death where appropriate.

Notably, the prevalence of suicidal ideation, suicidal behavior, and death by suicide all increase dramatically during the adolescent transition – a unique developmental vulnerability period for suicidal ideation and behaviors (Curtin et al. 2016; Glenn et al. 2017b; Kõlves & de Leo 2017). Attempts to explain and ultimately prevent suicide require a developmentally-informed framework to identify the emergence of novel risk factors, or developmental transactions between intra- and interpersonal risk factors unique to the adolescent period that elucidate why suicidal ideation and behaviors are more likely to appear within this age period than any other period in the lifespan (Nock et al. 2008, 2013).

This review is divided into three sections. Recently, several theoretical (Glenn et al. 2017a), systematic (Cha et al. 2017), and meta-analytic reviews (Franklin et al. 2017; Glenn et al. 2018; Ribeiro et al. 2016) have been published on the topic of suicide, with one review by Cha and colleagues focusing specifically on youth. In this manuscript, we first summarize these reviews and comment briefly on implications for current understanding of suicidal ideation and
behaviors in adolescence. Here, we also discuss conceptual frameworks previously offered to understand suicide and discuss limitations of each theory for explaining the onset of suicidal ideation and behavior in adolescence.

Second, this review considers current trends in research on adolescent suicide, with a specific focus on emerging biological markers. In this section, we offer a heuristic framework to interpret extant research and suggest targeted areas for future work. We suggest that adolescent suicidal crises may result from failures of acute biological stress response systems. Extant findings pertaining to each of several biological stress response systems are reviewed to offer a foundation for understanding the processes that may occur immediately prior to adolescents’ suicidal behavior and to guide future research. Last, we highlight some important questions suggested from emerging research on biological markers that have relevance for future research and treatment.

Our focus on acute stress response systems is designed to address a central limitation in prior work on suicide. For over six decades, research on suicide predominantly has focused on distal risk factors that are associated with an increased likelihood of suicidal ideation, behavior, or death by suicide months, years, or even decades later (Franklin et al. 2017). This research tradition has offered valuable insight for understanding putative preconditions and identifying possible risk groups for later suicidal ideation and behaviors. Unfortunately, this focus on distal risk factors is limited in three critical ways that may ultimately impede progress towards preventing and identifying effective treatments to reduce suicide.

First, most risk factors previously identified are remarkably weak predictors of later suicidal ideation and behavior. Of all individuals who have experienced each risk factor (e.g., depression, substance use, child maltreatment), very few will ever report suicidal ideation or
attempt suicide. Second, many prior conceptual frameworks and identified risk factors lack specificity; many elucidate risks relevant to psychopathology more generally, rather than to suicidal ideation and behaviors. Last, most suicidal behavior among youth occurs in response to a discrete stressful precipitant (King & Merchant 2008). Yet, prior work has not elucidated the biological or psychological processes that immediately follow stressful experiences and occur within the hours, minutes, or seconds prior to suicidal behavior. This review focuses on processes that may represent proximal risk factors, differentiating risks for general distress from those that may be most relevant to adolescents’ suicidal ideation and behavior. Importantly, our goal is not to explain every occurrence of adolescent suicidal ideation or behavior, but rather to offer a framework for exploring processes that may be most relevant for understanding why some distressed youth may elect to consider or attempt suicide, and why this becomes especially more likely during the adolescent transition.

**Correlates, Risk Factors, and Theories of Suicide**

Published papers on the onset, course, demographic characteristics, correlates, and risk factors for suicidal ideation and behaviors have steadily increased since the early 1980’s with nearly half of extant empirical studies published within the last 10 years (Franklin et al. 2017). Across time, far fewer empirical studies have been published on adolescent suicide compared to adult suicide (Franklin et al. 2017).

**Current Knowledge About Correlates and Risk Factors**

Many recent reviews and meta-analyses have offered summaries of current knowledge regarding predictors of suicidal ideation and behaviors (Cha et al. 2017; Franklin et al. 2017; Glenn et al. 2017a, 2018; Ribeiro et al. 2016). Remarkably, all of these reviews demonstrate that we know surprisingly little about the etiology of adolescent suicidal ideation and behaviors and
that predictors of suicidal ideation, suicidal behavior, and death by suicide are surprisingly weak.

For instance, Cha and colleagues (2017) offer a helpful catalog of correlates and risk factors for adolescent suicide across environmental, psychological, and biological domains, differentiating those factors that appear to prospectively predict suicidal ideation and behaviors beyond known predictors (e.g., depression and prior suicidal ideation or behaviors) from those that have been associated with suicide only concurrently. Results from this review suggest that beyond demographic characteristics, only childhood maltreatment, peer victimization, feelings of worthlessness, and low self-esteem increase risk for suicidal ideation or behaviors over time, after accounting for depression and prior suicidal ideation or behaviors as predictors (Cha et al. 2017). While these risk factors provide information about global risk for any suicidal ideation or behaviors in the future, they are nonspecific. In other words, they do not provide information about which youth are more vulnerable to these risk factors or when a given youth will experience suicidal ideation or engage in suicidal behavior. Further, it is not clear how these factors confer risk in the proximal moments of a suicidal crisis.

Meta-analytic reviews of the broader suicide literature across the lifespan yield remarkably low odds ratios in the prospective prediction of suicidal ideation or behaviors. For example, they note that while internalizing risk factors accounted for nearly 66% of all predictors examined in the literature, they were not strongly related to future risk for suicidal ideation or behaviors when omnibus effect sizes are considered in meta-analyses (odds ratios between 1.17 and 1.71; Franklin et al. 2017). Similarly, Glenn and colleagues (2018) revealed significant, but low effect sizes for markers of the RDoC Negative Valence System domain (i.e., depressed mood, rumination, and hopelessness) in the prediction of suicidal ideation or behaviors. Even the effects of prior suicidal ideation and behaviors are relatively weak in the prediction of future
suicidal behavior (Ribeiro et al. 2016) reflecting that only a minority of those who attempt suicide are likely do so again in most studies.

Together, these reviews highlight a fundamental limitation in the suicide literature; by focusing on distal risk factors, it has been remarkably difficult to identify predictors of suicidal ideation, behaviors, or death by suicide that are robust. Consequently, little is known regarding the processes that may immediately precede suicide, and few effective strategies designed to intervene in the hours or minutes before individuals engage in suicidal behavior are available (Asarnow et al. 2017; Cha et al. 2017; Miller et al. 2017a), perhaps particularly among youth. To date, only three randomized control trials have demonstrated efficacy in temporarily reducing risk for suicidal behavior among adolescents with a past history of suicide attempts or self-harm (Asarnow et al. 2017; Esposito-Smythers et al. 2011; McCauley et al. 2018).

Theories of Suicide

Given that suicidal behavior runs counter to the basic biological instinct to survive that is present even in single-celled organisms, there has been no shortage of theories offered to explain the conditions under which this perplexing behavior occurs, dating as far back as the ancient Greek writings of Plato and Aristotle. Rarely do these theories offer insight regarding developmental factors that may make adolescence a unique vulnerability period for suicidal ideation and behaviors.

In contemporary work, however, most theories reflect at least one of three themes that many consider central to the experience of suicide, particularly within the moments that immediately precede suicidal behavior. First, past theoretical work highlights the relevance of interpersonal distress as perhaps uniquely relevant to individuals’ decisions to engage in suicidal behavior. For instance, Durkheim’s (1897) well-cited theory from the late 19th century first
highlighted the important role of social integration as a key factor associated with the desire to engage in self-inflicted injury. Baumeister’s (1990) escape theory similarly suggested that following realization about the self’s social inadequacies and interpersonal failures, individuals turn to suicide to escape resulting emotional distress. Shneidman (1993) asserted that suicide emerges from “psychache” or mental pain, partly caused by social isolation. More recent theories also have emphasized negative interpersonal states that give rise to suicidal thinking (Joiner 2005; Klonsky & May 2015; O’Connor 2011; Van Orden et al. 2010), including thwarted belongingness or perceived burdensomeness.

Second, most theories suggest that suicidal ideation and behaviors are an expression of affective distress, perhaps resulting in cognitive inflexibility. Menninger (1933) suggested that suicide was a coping strategy to reduce extreme pain and self-blame. Neuringer (1964) noted that suicidal individuals were characterized by rigid thinking. Linehan (1993) highlighted the role of emotional dysregulation preceding suicide, and both Baumeister (1990) and Beck (1987) posited that increasingly distorted thinking leads an individual to view destructive behaviors as a reasonable option for dealing with intolerable distress. Recent work has suggested that dysfunctional cognitions related either to stressor appraisals or more generally to self-worth may be relevant predictors for later suicidal behavior (Klonsky & May 2015; Van Orden et al. 2010).

Last, some theories of suicide have attempted to link the exposure to stressors and the affective or cognitive experience of distress, with engagement in specific behaviors that may increase risk for suicidal behavior. For example, cognitive and dialectical behavioral theories of suicide suggest that distorted thinking often leads to narrowed problem-solving abilities and risky or self-regulatory behavior, such as alcohol use or self-harm, that may make future suicidal behavior more likely (Linehan 1993; Rudd 2010; Spirito et al. 2012).
Naturally, the exposure to stress and experience of cognitive-affective distress has biological concomitants as well, although few theories acknowledge biological underpinnings in the etiology for suicide. One notable exception is Linehan’s (1993) theory of suicidal behavior suggesting that abnormal biological signaling subsequent to stress, such as increased heart rate, rapid breathing, and general agitation, may increase perceptions of distress, leading individuals to engage in self-harm behaviors as a strategy for self-regulation. In addition, Joiner’s Interpersonal-Psychological Theory posits that a person’s ability to enact lethal self-harm is acquired throughout the lifetime, with potentially dangerous or near-fatal prior experiences changing the body’s biological response to self-harm, resulting in a greater likelihood of eventual death by suicide (Van Orden et al. 2010).

These biological processes may be especially pertinent in adolescence, a developmental period characterized not only by increased exposure to interpersonally-themed stressors, but also a recalibration of acute stress response systems. We argue that in order to understand the course of suicidal ideation and behavior across the lifetime, we first must understand why adolescence represents a critical time of vulnerability.

Adolescence: A Critical Time of Vulnerability to Suicide

As reviewed above, few developmentally-based theories have been offered to help explain why suicidal ideation and behaviors increase in prevalence at the adolescent transition (Nock et al. 2013). In this section, we offer an overview of unique social, and biological processes that occur in adolescence that may help explain the unique vulnerability period for suicide. First, we briefly review biological and social changes that occur during adolescence. Next, we discuss four biological systems related to typical stress responses (i.e., the autonomic nervous system [ANS], hypothalamic-pituitary-adrenal [HPA] axis, peripheral stress responses,
and neural responses within the brain) and review extant theory and data regarding how these systems change during adolescence. We then review available research on markers of acute stress response systems that have been associated with suicidal ideation, behavior, and death by suicide. Finally, we discuss our conceptualization of a developmentally-informed framework highlighting two potential moderators of the relationship between dysfunctional acute stress responses systems and suicide among youth.

The Adolescent Transition

Adolescence is marked by dramatic changes in biological and social systems that simultaneously increase acute stress response system reactivity and adolescents’ orientation towards social stimuli creating a uniquely vulnerable time frame for the emergence of suicidal ideation and behavior. The onset of puberty, characterized by rapid external physical and internal biological changes, includes extensive neural network changes in the brain and alterations in hormonal systems as adolescents move towards sexual maturity (Gunnar et al. 2009; Rudolph 2014; Susman & Dorn 2009). However, neural development is localized within specific regions of the brain across development. Early within this process, beginning before physical manifestations of puberty are evident, changes within the limbic system include synaptic pruning, increased myelinization, and a proliferation of dopamine and oxytocin receptors that facilitate more rapid and dramatic responses to social rewards and avoidance of social punishment (Casey et al. 2008; Chein et al. 2011). Throughout puberty, changes in social and mentalizing neural networks allow for more sophisticated social comparisons and reflected appraisals, allowing adolescents to form a more stable sense of self-concept that is heavily dependent on perceived peer appraisals (Casey et al. 2008; Harter et al. 1996; Somerville 2013). Comparable changes in prefrontal cortical development allowing for emotional regulation skills
and goal directed behavior do not occur until years later. In sum, findings from developmental affective neuroscience suggest that adolescents experience several years during the pubertal transition with newly developed and robust responses to their social environment, a more sophisticated capacity to allow these social experiences to shape their self-concept, but without mature abilities to regulate their emotions or inhibit impulsive responses (Casey et al. 2008). Research confirms that adolescents experience increased physiological responses to stressors (Stroud et al. 2009), increased prefrontal brain activation during social evaluation (Somerville 2013), and struggle to implement cognitive control skills in the context of emotionally evocative events (Cohen et al. 2016; Somerville et al. 2011). Interestingly, epidemiological data suggest that youth between 12 and 17 years of age also reflect the most dramatic increase the incidence of suicidal ideation and behavior (Nock et al. 2013).

These biological changes occur in parallel to notable alterations in adolescents’ peer milieu and in the frequency and quality of adolescents’ social experiences. Note that in many cultures, the pubertal transition is timed with a school transition and the introduction of a larger peer group, requiring adolescents to navigate more complex social roles and novel peer relationships. In recent years, adolescence also is associated with an increase in adolescents’ online interactions with peers, offering remarkably frequent opportunities for new forms of interpersonal relationships and social expectations (Nesi et al. 2018). Indeed, research suggests that the pubertal transition is associated with marked increases in adolescents’ interactions with peers, concomitant decreases in parental supervision, and more severe parent-child conflict (Prinstein & Giletta 2016). At the peer group level, adolescence is marked by the introduction of a new form of peer status, reflecting adolescence’ dominance, power, influence, and visibility (Cillessen & Rose 2005; Parkhurst & Hopmeyer 1998). Adolescents’ bids to enhance or maintain
this form of peer status frequently involve the use of overt or relational aggression strategies that often are cited as powerful predictors of adolescent suicide (Juvonen & Graham 2014; Massing-Schaffer et al. 2018). Adolescence also is marked by an increase in the frequency and emotional intimacy of dyadic peer experiences, with both best friendships and emerging romantic relationships occupying more of adolescents’ attention and interest (Rose & Rudolph 2006; Steinberg & Morris 2001). These dyadic relationships can be a significant source of stress. As compared to children and adults, adolescents report higher levels of peer-related interpersonal stressors and greater emotional reactivity to these types of stressors (Rudolph 2014). Note also that these peer-related stressors (e.g., friendship alienation, romantic break-ups, bullying) are among the most frequently reported precipitants to adolescents’ suicidal behavior (Juvonen & Graham 2014; King & Merchant 2008; Massing-Schaffer et al. 2018).

In sum, the adolescent transition offers a potentially risky person-environment transaction that may be especially relevant for understanding suicide. Biologically equipped with an increased investment in social interactions and enhanced social sensitivity, adolescents enter a world involving novel, complex, and unfamiliar social interactions with increased stakes for success, but immature biological resources to adequately regulate social stress. Indeed, difficulties navigating this unique combination of adolescents’ changing environmental context, developing self- and social competencies, and biological vulnerabilities have been associated with a range of psychological symptoms and adjustment difficulties (see Prinstein et al. 2018, for a review). Suicidal ideation and behavior may follow particularly severe social stressors, particularly among those with atypical acute biological stress response systems. Below, we discuss acute biological stress response systems, how these systems change in adolescence, and we also briefly note why these responses may develop atypically among some youth.
**Typical Acute Biological Stress Responses**

Adolescence also is associated with a recalibration of acute biological stress response systems that may further create a developmental vulnerability period for suicide. This notion has been recognized only recently, however, through emerging work on the nature of acute biological stress systems and the way that each of these systems may evolve across the pubertal transition. In this section, we briefly review acute stress responses and physiological markers in the ANS, HPA axis, peripheral stress response systems, and neural networks. Following this brief overview, we discuss current knowledge regarding the specific changes that occur within each of these in adolescence.

The ANS and HPA Axis represent two hormone systems that act to mobilize the body to act flexibly and adaptively in response to a stressor. The fast-acting sympathetic branch of the ANS (SNS) releases epinephrine and norepinephrine into the bloodstream activating the “flight-or-fight” response to a stressor. This system is modulated by the parasympathetic branch of the ANS (PNS) which has been specifically implicated in self-regulatory processes (Beauchaine 2015). The PNS exerts control of heart rate via the vagus nerve (Porges 2007), and its influence is measurable via respiratory sinus arrhythmia (RSA). RSA reflects the ebbing and flowing of the heart rate across the respiratory cycle (Beauchaine 2015; Porges 2007), with increased inhibitory PNS signaling during exhalation and decreased inhibitory PNS signaling during inhalation. In this way, PNS acts as a break on the sympathetic nervous system by reducing heart rate and facilitating alert engagement in the environment (Porges 2003, 2007). When an individual is faced with threatening or emotional stressors, PNS withdrawal (indexed via RSA decreases or RSA suppression) occurs almost instantaneously thereby facilitating the fight or flight response of the SNS. Dynamic and flexible responses of RSA across environmental
contexts are essential for adaptive physiological self-regulation (Hastings et al. 2014).

The second, slower acting stress response by the HPA axis begins in a group of neurons, the paraventricular nucleus (PVN), within the hypothalamus. The PVN stimulates the release of corticotropin-releasing hormone, which signals the pituitary gland to release adrenocorticotropic hormone (ACTH). ACTH acts on the adrenal glands to synthesize and release glucocorticoids. Glucocorticoids (cortisol in humans) are the end point of the HPA axis system and are responsible for many of the adaptive acute stress responses, such as enhanced memory (Barsegyan et al. 2010) and regulation of inflammatory immune signaling (Slavich & Irwin 2014). Operating in a negative feedback loop, glucocorticoids signal the HPA axis to shut off following the end of a stressor via targeted brain structures, including the PVN, hippocampus, amygdala, and prefrontal cortex (PFC) regions (Herman et al. 2003; Tasker & Herman 2011).

In addition to these two central acute stress response systems, peripheral stress responses systems, including the immune system, polyamine system, and cellular level processes (including gene expression), activate following exposure to an acute stressor to prepare the body for adaptation and recovery after a stressor has passed. The body’s adaptive immune response to a stressor triggers pro-inflammatory activity which promotes signaling of intracellular transcription. This transcription ultimately drives the activity of intracellular, proinflammatory immune response genes (e.g., tumor necrosis factor-α [TNF-α] and interleukin-1 [IL-1]) that release protein molecules called cytokines, which are the primary mediators of systemic inflammation (Raison et al. 2006; Slavich et al. 2014). Further, the end products of the SNS (norepinephrine) and HPA axis (cortisol) interact with immune cells in the body leading to increased inflammatory activity (Raison et al. 2006; Slavich & Irwin 2014).

Polyamines are aliphatic molecules that are stress-responsive (Gilad & Gilad 2003), play
a major role in homeostatic regulation, and function to influence neurotransmitter systems, including catecholamines, gamma-aminobutyric acid (GABA), glutamate, and nitric oxide (for excellent review see Gross & Turecki 2013). Polyamine levels increase following exposure to stress, and the magnitude of this response is associated with the intensity of the stressor and behavioral response to the stressor (Gilad & Gilad 2003; Turecki 2014). Though still an emerging area of research, cellular level responses to acute stress, such as free-circulating mitochondrial DNA (mtDNA), results in downstream systemic inflammation (Picard et al. 2014).

Of course, the stress responses also can be tracked through neural networks that are triggered, regulated, and terminated within the brain. The vagus nerve modulates the faster acting sympathetic branch of the ANS and transmits afferent signals to subcortical structure of the brain including the amygdala via the nucleus tractus solitarius (Berthoud & Neuhuber 2000). Glucocorticoids, the end product of the slower acting stress-response system, signal the HPA axis to shut off via targeted brain structures, including the PVN, hippocampus, amygdala, and PFC regions (Herman et al. 2003; Tasker & Herman 2011). Peripheral inflammation is similarly controlled via subcortical neural structures, including the hypothalamus (Sternberg 2006).

Although data from studies in developmental affective neuroscience are still emerging, accumulating evidence suggests that pubertal adaptations in acute stress response systems likely contribute to a protracted period of increased stress reactivity and prolonged stress responses (i.e., slower return to baseline) in adolescence - at the same developmental period associated with greater exposure to interpersonal stress (Dahl & Gunnar 2009). For example, across rodent and human studies, adolescents demonstrate changes in ANS responses, including increased SNS reactivity and PNS withdrawal to acute stressors (Allen & Matthews; Choi & Kellogg 1996; Kurtz & Campbell 1994; Stroud et al. 2009), suggesting that adolescents are more
physiologically reactive to stressors and less able to flexibly regulate these increased signals. Similarly, changes in the HPA axis during adolescence result in heightened cortisol reactivity to acute stressors and a longer recovery relative to childhood and adult years (Gunnar et al. 2009; Romeo 2017). Less is known regarding adolescent specific changes in peripheral stress response systems, though research has begun examining typical adolescent levels of immune system markers, such as cytokines (Riis et al. 2014). Evidence from neuroimaging research demonstrates increased neural reactivity to negative stimuli during adolescence relative to children and adults (Silvers et al. 2012) and increased social sensitivity reflected by activity in the anterior cingulate cortex among adolescents, as compared to children or adults (Somerville 2013; Somerville et al. 2013). Together, normative adolescent development is defined by increased sensitivity and responsiveness across these acute stress response systems and recent data suggest that atypical presentations of these same systems have implications for understanding emotion dysregulation (Miller et al. 2017b; Tottenham et al. 2010) and a range of both internalizing and externalizing symptoms (Burghy et al. 2012; Chen et al. 2015; Nederhof et al. 2015; Slavich & Irwin 2014).

Although a full discussion of factors that lead to the development of atypical biological stress response systems is beyond the scope of this review, note that many of the same factors that have been identified as distal predictors for suicide (e.g., depression, child maltreatment, etc.) also have been associated with dysfunctional acute stress responses in adolescence. For instance, a rich literature has demonstrated that depressive symptoms are associated with the development of hyporeactive responses to stress in the HPA axis (See Guerry & Hastings 2011 for a review). Research also indicates that exposure to chronic stress during early development has lasting effects on stress responses (see McEwen & Gianaros 2010 for a review). Findings
from rodent studies and human neuroimaging research have revealed that early chronic stress is linked with increased amygdala reactivity and with a lack of prefrontal regulation to acute stressors (Tottenham & Galván 2016). Rodent models also have demonstrated that chronic exposure to stress, particularly during early childhood and adolescent development, is associated with structural and functional changes in both the amygdala and hippocampus increasing risk for altered acute stress responses (Radley et al. 2015).

**Associations Among Biological Markers of Stress Response and Suicide**

Although data on adolescents is sorely lacking, extant research suggests that each of these biological stress responses systems may be linked with suicidal ideation and behaviors. We believe this is a critical direction for future research to identify the proximal processes that occur between individuals’ experience of stress and the decision to engage in suicidal behavior. Ideally, this research would use experience-sampling procedures, short-term longitudinal designs, and in vivo assessments to capture actual acute stress responses. However, note that unique methodological (and ethical) limitations make the study of suicide more challenging than perhaps the examination of most every other clinical phenomenon. Thus, findings remain sparse, particularly among adolescents. Below we review preliminary associations between suicide and markers of the two central acute stress response systems, the ANS and the HPA axis. Then, we move to genomic markers of peripheral stress response systems. Finally, we discuss neural markers emphasizing that stress responses initiate and terminate in the brain.

**Markers of Central Stress Response Systems**

**ANS.** Though still an emerging area of research in the adolescent suicide literature, a handful of studies have examined RSA as an ANS correlate of suicide risk, with findings suggesting that lower resting RSA or excessive RSA withdrawal may be linked with emotion
dysregulation and suicidal ideation and behavior. However, findings have been mixed, suggesting that more research is needed, particularly among youth.

In general, findings from concurrent studies, examining individuals with and without lifetime histories of self-injury have been promising. For instance, in an early concurrent study, adolescent females with either a history of suicidal behavior and/or NSSI ($N = 23$, ages 14-18) evidenced lower resting RSA and excessive RSA withdrawal (i.e., greater release of SNS suppression) following exposure to evocative stimuli compared to controls ($N = 23$, ages 14-18) (Crowell et al. 2005). Another study demonstrated that children (ages 7 -11) with a history of suicidal ideation and who have parents rated high on expressed negative emotion did not show flexible RSA responses to a stressful discussion, suggesting poor adaptive stress-response (James et al. 2017). Evidence from adult studies also suggest that lower resting RSA is associated with suicidal ideation (Rottenberg et al. 2002) and distinguishes individuals with and without a suicide attempt history (Tsypes et al. 2018).

However, studies examining RSA as a prospective predictor of later suicidal ideation and behavior have yielded more equivocal findings. In a sample of community-based early adolescents ($M$ age = 12.82), Weigus and colleagues (2016) revealed that resting RSA and greater RSA withdrawal to a non-interpersonal frustration task did not predict engagement in self-injurious thoughts and behavior (defined as a composite of NSSI, suicidal ideation, and suicidal behavior) over the following six months. However, lower recovery of RSA (indexed by lower resting RSA during the recovery from the task) was associated with prospective risk for this same self-injury composite over time (Wielgus et al. 2016). In contrast, Giletta and colleagues (2017) revealed that greater RSA withdrawal following a social stressor task was associated with prospective risk for suicidal ideation over the following nine months in a sample
of adolescents with a history of mental health concerns, even after controlling for lifetime history
of suicidal ideation and current depressive symptoms. More research examining RSA indices in
response to interpersonal and non-interpersonal stress across different developmental periods
may be especially important to understand whether suicide may be predicted by dysregulated
arousal or recovery following stress. However, findings offer preliminary promise suggesting
that ANS responses to acute stressors may provide insight into adolescents’ risk for suicide.

**HPA Axis.** Researchers also have recently indexed markers of the HPA axis as potential
predictors of suicidal ideation and behavior. Notably, this has involved the examination of
baseline/resting salivary cortisol levels, chronic cortisol output as measured by hair cortisol
concentrations, and reactive cortisol through repeated salivary sampling before, during, and after
an experimentally-induced stressor. Unfortunately, little work has been done with adolescents.

Regarding baseline cortisol, both hyper- and hypo-cortisol levels have been associated
with suicide. For instance, in some studies with adults, elevated levels of baseline cortisol levels
have been associated with greater frequencies of suicidal behavior (Mann & Currier 2007). Yet,
in more recent studies with combined samples of adults and youth, individuals with a lifetime
history of suicidal behavior have had lower levels of baseline or hair concentration cortisol
compared to individuals with only suicidal ideation or healthy controls (Keilp et al. 2016;
Melhem et al. 2017).

Findings regarding cortisol levels following a stressor similarly reveal that both hypo-
and hyper-reactivity may be relevant for suicide. In cross-sectional study of depressed and/or
self-harming adolescent girls, lower post-dexamethasone suppression test cortisol (suggesting
cortisol hypo-reactivity) was associated with greater current suicidal ideation (Beauchaine et al.
2015). Some studies have revealed that adults with a history of suicide attempts have more
blunted cortisol reactivity to a Trier Social Stressor Task (TSST) than those with suicidal ideation histories alone or healthy controls (Melhem et al. 2016; O’Connor et al. 2017).

Other than research from our own research group, we are unaware of any other studies examining cortisol reactivity to social stressors as a prospective predictor of suicidal ideation and behavior among adolescents. Our research examined cortisol reactivity to a social stress task (TSST) in a sample of adolescent girls (ages 13-17) at elevated risk for future suicide due to a history of mental health concerns. Following the lab-based stressor, participants were followed quarterly for 18 months to examine cortisol reactivity as a prospective predictor of adolescent suicide ideation and attempts. Initial findings revealed a significant effect for cortisol hyperreactivity (and a marginal trend for hypo-reactivity) to the TSST on risk for suicidal ideation three months later, even after controlling for lifetime histories suicidal ideation and other distal risk factors (e.g., impulsivity) (Giletta et al. 2014). Subsequent analyses using a multi-level model to capture within-person deviations in chronic peer stress revealed that higher-than-usual peer stress predicted suicidal ideation over 18 months regardless of HPA axis function, but predicted suicidal behavior only among girls with blunted cortisol responses to the TSST at baseline (Eisenlohr-Moul et al. 2018b).

In sum, as a marker of HPA axis responses to stress, extant findings suggest that dysregulated cortisol levels maybe a relevant marker of suicide risk. Consistent with allostatic load theories (McEwen 2007) regarding moderate levels of cortisol facilitating flexible, adaptive responses to environmental stressors, findings suggest that both hyper- and hypo-cortisol responses reflect disruptions in the HPA axis system that may increase vulnerability to suicide in the context of acute stress.

Peripheral Stress Response Systems and Functional Genomics
Markers of several peripheral responses systems also may be relevant correlates of adolescent suicide. Recent efforts have focused on epigenetic mechanisms, with far more research examining cytokines than other peripheral response markers to date. Below we review some of the promising findings related to cytokines followed by preliminary work linking suicide with polyamines, mitochondrial DNA, and other epigenetic markers.

**Cytokines.** Recall that the immune system responds to acute stressors resulting in increased inflammation aimed at promoting healing and recovery. Following acute stressors, proinflammatory cytokines signal the brain to engage in sickness behaviors closely mimicking depression and in some cases leading to clinical depression among physically ill people (Dantzer et al. 2008). With work demonstrating that adverse social experiences characterized by loss or threat activate proinflammatory cytokine activity (Giletta et al. 2018; Slavich & Cole 2013) and trigger alterations in genes regulating pro-inflammatory cytokine production (Slavich et al. 2010), increased inflammatory brain signaling in the context of exposure to social stressors may distinguish adolescents at risk for suicidal ideation and behavior.

This hypothesis has some support from emerging studies demonstrating increased proinflammatory cytokine activity in individuals with suicidal ideation and behavior as compared to controls (Black & Miller 2015). Findings indicate that adults with a history of suicidal behavior show increased levels of interleukin-6 (IL-6) (Janelidze et al. 2011; Lindqvist et al. 2009; Serafini et al. 2013), increased TNF-α (Janelidze et al. 2011), decreased levels of IL-2 (Janelidze et al. 2011; Serafini et al. 2013), and increased cytokine-stimulated plasma kynurenine (Sublette et al. 2011) and quinolinic (Erhardt et al. 2013) acid levels in cerebrospinal fluid (CSF).

Results linking cytokines to suicidal ideation or behavior among adolescents are rare, but
findings are promising. For instance, one study revealed that adolescents with major depressive disorder and suicidal ideation ($N = 12$) showed higher levels of interferon-$\gamma$ compared to controls ($N = 15$) (Gabbay et al. 2009). In a sample of adolescents and emerging adults (age range 15-30), individuals with suicide attempt histories had higher levels of TNF-$\alpha$ and C-Reactive Protein compared to those with suicidal ideation histories and healthy controls (Melhem et al. 2017). In another study, youth who died by suicide ($N = 24$) compared to matched healthy controls ($N = 24$) had higher levels of IL-6, IL-1$\beta$, and TNF-$\alpha$ in the prefrontal cortex (PFC) (Pandey et al. 2012), suggesting that pro-inflammatory cytokines may be a useful avenue for further exploration of adolescent suicide risk.

**Other Epigenetic Markers.** Preliminary results also have been revealed for associations between suicide and polyamines, mDNA, and DNA methylation. The polyamine system has been implicated in risk for suicide (see Lutz et al. 2017 for a detailed discussion) with preliminary empirical findings coming from rodent studies and postmortem studies of human adults. For example, one study revealed that administration of the polyamine agmatine ameliorated experimentally (TNF-$\alpha$)-induced depression-like behaviors in mice (Neis et al. 2014). Altered polyamine-related genes, suggesting system dysregulation, also was revealed in a postmortem studies of adults who died by suicide (Gross & Turecki 2013). Both studies suggest that the polyamine system may be relevant for regulating depressed affect and perhaps also suicidal ideation or behavior. Results on mDNA similarly suggest that dysregulation may be linked with suicide. In a recent study of adults, free circulating mtDNA measured via blood plasma was significantly higher in individuals with a suicide attempt history compared to healthy controls (Lindqvist et al. 2016). Researchers have found that DNA methylation systematically alters gene expression resulting in increased risk for psychopathology and specifically suicide
(Haghighi et al. 2014). There is also some preliminary evidence for autonomic dysregulation in insulin and glucagon secretion among individuals with suicide attempt histories (Bendix et al. 2017). Further examination of peripheral stress system markers in the context of suicide will be an important direction for future work.

**Neural Markers**

Emerging research in neuroscience supports a link between suicide risk and altered neural structure and function. Subcortical brain structures, which mediate acute stress responses, are modulated and regulated via prefrontal brain regions. Altered frontolimbic connectivity could help explain why some youth who experience an acute stressor are unable to leverage higher order skills, such as cognitive reappraisal (Buhle et al. 2014), to modulate subcortical activation, and subsequently begin experiencing suicidal ideation. Examinations of both subcortical and cortical brain structure, neural activation, and network connectivity have revealed preliminary associations with suicide risk.

Subcortical brain regions, including the amygdala and hippocampus, are primitive brain structures that monitor the environment for salient cues for reward or threat. In particular, these structures play an important role in the perception of stressors and signal the body to enact and modulate stress responses. Thus, altered structure and function in these areas may engender risk for altered acute stress responses. Two recent studies suggest youth at risk for suicide demonstrate significant differences in subcortical brain regions. Johnson and colleagues (2017) revealed that as compared to non-suicidal controls, youth with lifetime histories of suicidal behavior had decreased grey matter volumes in the hippocampus and cerebellum and decreased functional connectivity between the amygdala and left ventral and right rostral PFC when viewing emotional faces (Johnston et al. 2017), suggesting altered signaling between subcortical
and PFC control regions. Another study by Quevedo and colleagues (2016) found that youth with histories of suicidal ideation and behavior demonstrate blunted responses to happy faces in the hippocampus and amygdala suggesting altered processing of potential stressors in the environment. Together, early evidence suggests altered signaling in subcortical regions among youth at risk for suicide.

The PFC serves a critical role in leveraging higher order cognitive skills in the service of modulating subcortical activation. In other words, the PFC can assist in managing subcortical activation resulting from exposure to a stressor to achieve an efficient and effective acute stress response. An emerging line of research points to altered neural activation (Just et al. 2017; Miller et al. 2018; Pan et al. 2013; Quevedo et al. 2016) and neural network connectivity (Chase et al. 2017; Ordaz et al. 2018; Zhang et al. 2014, 2016) in PFC regions among individuals with histories of suicidal ideation or behavior. For instance, work from our group demonstrated that as compared to controls, youth with a history of suicidal ideation show decreased dorsolateral prefrontal cortex (dlPFC) activation compared to youth without suicidal ideation when passively viewing negative stimuli (Miller et al. 2018), suggesting that youth with SI histories may not automatically engage skills to regulate negative emotions. With regard to functional connectivity, individuals with suicidal ideation histories appear to show abnormal resting state connectivity between PFC control regions and subcortical brain regions (Chase et al. 2017; Ordaz et al. 2018), potentially signaling a vulnerability to increased reactivity and decreased ability to modulate this reactivity when faced with a stressor. In adult samples, similar findings have emerged suggesting decreased frontolimbic functional connectivity in individuals with suicidal ideation (Du et al. 2017; Kim et al. 2017; Minzenberg et al. 2015). Together, available research suggests that activation of the PFC and subcortical regions during emotionally evocative
tasks may be associated with suicidal ideation and behavior among adolescents.

Though more research is needed in the area of neural underpinning of suicidal ideation and behavior among youth, emerging evidence points to altered activation and connectivity patterns that may have specific effects on subcortical activation, which are instrumental in mediating and modulating acute stress response systems. Notably, the PFC is a relatively large region, and findings have not yet converged on one specific structure within the PFC. Further, the data is not yet consistent enough to distinguish neural markers of risk for suicidal ideation from risk for suicidal behavior. This is an area in critical need of future research as neural processes underlying suicidal ideation are likely related but different from those underlying suicidal behavior. Further, none of these studies examine prospective risk for suicidal ideation and behavior.

**Synthesis and Future Directions**

In this review, we have suggested that our understanding, and ultimately successful prevention/treatment of suicide would be aided by addressing one of the central facts about this perplexing and troubling clinical phenomenon – namely, the worldwide trend for suicidal ideation and behavior to increase dramatically in prevalence at the adolescent transition (Nock et al. 2013); a fact that unfortunately has been unaddressed in most all prior theories regarding suicide. We have reviewed a constellation of biological and social adaptations to adolescence that occur at precisely the same period when the onset of suicidal ideation and behavior is most likely to occur. Also, consistent with dynamic systems theories, we elucidated how reciprocal intra- and interpersonal transactions between social-environmental, cognitive, and biological systems may confer a unique risk for the types of interpersonally themed-stress that most adolescents report as precipitants to suicidal behavior, and the impulsive suicidal urges that are
more common among adolescents than among suicidal adults (Orbach 1997).

With this review, we also have encouraged a greater focus on biological acute stress responses that may help explain proximal processes occurring in the moments between adolescents’ exposure to stress and their experience of suicidal ideation and behavior (see also Cha et al. 2017; Chang et al. 2016; Lutz et al. 2017; Pan et al. 2011, 2016; Turecki & Brent 2016). Four biological systems that are implicated in acute stress responses have been discussed, with a summary of evidence to date suggesting that each 1) may undergo important recalibration in adolescence, increasing vulnerability during this developmental period; 2) may be especially dysregulated among adolescents who possess known distal risk factors for suicide; and 3) are associated with relevant suicidal outcomes, at least preliminarily based on available, albeit limited empirical studies to date.

In sum, we have suggested a heuristic model to guide further research (see Figure 1). This model suggests that compounding vulnerability conferred from the pubertal transition and from pre-existing distal risk factors affect biological stress response systems in adolescence, leaving some youth especially ill-prepared to cope with the increase in interpersonal stressors that characterize this developmental period. Note, however, that it remains unclear why these distressed adolescents exhibit suicidal ideation and behavior.

Indeed, the problem with this model, like so many others proposed to explain suicide, is the multifinality of the risk pathways we have articulated thus far. In short, many other domains of psychopathology also may be predicted by these same distal factors, the onset of social-biological adaptations to puberty, and atypical stress response systems. In short, why suicide? We propose that as compared to a host of other possible dysfunctional outcomes, suicide is most likely to occur when at least one of two conditions is met.
Stress Threshold

First, we posit that suicide may become more likely when individuals experience distress that is unusual, severe, and exceeds their actual or perceived capacity to activate cognitive and social coping resources. In other words, suicide may follow from the same stress response processes that confer risk for other forms of psychopathology when stressors exceed an individuals’ own stress threshold.

For healthy individuals, stress thresholds may be quite high. Yet, even healthy individuals with intact acute stress response systems might conceive of suicidal behavior if faced with a stressor perceived to be unusually intense, life-altering, or overwhelming (see Orbach 1997 for a detailed discussion of suicide attempters who exhibit high levels of perfectionism, but no other apparent psychopathology). For those with depressive symptoms, chronic or early childhood stress, or other distal risks for suicide, thresholds may be lower, however, making suicide a more likely option.

Although a rich literature exists examining the association between stress and suicide, most all prior research studies have employed analytic approaches that prohibit tests of a stress threshold hypothesis. Note that traditional tests of associations among suicide risk factors and self-injurious constructs traditionally utilize a between-subjects design, with resulting statistical indices revealing whether those high in stress compared to an entire study sample may also exhibit higher levels of suicidal ideation or behavior than others in the sample. Moreover, the vast majority of prior research on suicide is concurrent in nature, precluding the ability to understand how individuals’ experience of stress, or suicidal ideation or behavior at one time point might compare with an individuals’ enduring level of stress.

A series of multi-wave prospective studies using a within-subjects analytic approach
conducted within our research group has offered some evidence to support a stress threshold hypothesis. In a large sample of adolescent girls, we found modest between-person associations between interpersonally-themed stress and suicidal ideation or attempts over the course of an 18 month follow up period. However, our ability to predict when adolescents may attempt suicide was notably enhanced by computing individual stress and suicide trajectories, allowing us to examine how girls’ stress within each three-month follow-up period compared to their average (person-centered) level of stress across their entire participation in our study. Findings suggested that among adolescent girls who have been exposed to child abuse, for instance, periods of higher than usual stress are also times of enhanced risk for suicidal behavior (Miller et al. 2017a). Moreover, results revealed a social-biological transactional effect suggesting that suicidal attempts were most likely among girls who demonstrated a hyporeactive cortisol responses to a social speech task and only during period when they experienced higher-than-usual peer stress (Eisenlohr-Moul et al. 2018b). We have replicated a similar pattern of results in a separate sample of adolescents and in a sample of emerging adults (Miller et al, 2018).

**Suicide Propinquity**

A second factor that may increase the likelihood that vulnerable (i.e., stress-exposed) adolescents might exhibit suicidal ideation or suicidal behavior reflects the extent to which they have been exposed to suicide as an available option for ameliorating distress. While for many distressed individuals, suicide may seem like a remote consideration – an option that may not even enter consciousness, there are several factors that may increase the likelihood that adolescents will readily consider suicide, including 1) their own prior experiences with self-injury and suicide, such as prior NSSI, ideation, or attempts; 2) their knowledge of others’ (a relative’s or celebrity’s) suicidal behavior, or 3) peer socialization towards self-injurious
thoughts and behaviors. The notion of suicide propinquity is not novel, but rather represents an integration of substantial theory and empirical data. Adolescents who engage in NSSI or make suicide attempts are significantly more likely to engage in future suicidal behavior (Ribeiro et al. 2016), especially within the first few months following an attempt (Goldston et al. 2001). The effects of exposure to well-known individuals’ suicidal behavior on adolescents’ own suicidal behavior also has been well-documented through research on suicide clusters (see Brent et al. 1989; Gould 1990; Gould et al. 1990; Joiner 1999; Phillips & Carstensen 1986), yielding best practice recommendations for the media and school-personnel when covering the death by suicide of a well-known person (Pirkis et al. 2006).

A growing body of data also suggests that adolescents may be particularly susceptible towards socialization of self-injury when a close friend endorses depressive symptoms, NSSI, or suicidal ideation and behavior (Bearman & Moody 2004; Kandel et al. 1991; Rew et al. 2001; Yoder 1999). Although most prior studies have examined concurrent associations, making it difficult to determine whether adolescents select friends who are similarly suicidal, or are socialized towards greater suicidal ideation and behaviors through affiliations with other distressed teens, some emerging longitudinal evidence suggests that friends’ suicide is a meaningful predictor of adolescents’ own risk for future NSSI (Giletta et al. 2013; Prinstein et al. 2010; You et al. 2013) and suicidal behavior (e.g., Liu 2006).

Thus, suicide propinquity may moderate the association between adolescents’ acute stress response and suicidal ideation or behavior. Although many adolescents with developmental risk factors may experience psychological symptoms following stress, those who become suicidal might be predicted by understanding whether adolescents have recently been exposed to, and perhaps consequently possess less aversive attitudes towards suicide (Nock et al. 2010).
Conclusions

In conclusion, this integrative review has offered several new directions for research on adolescent suicide aimed at better understanding a phenomenon that has remained poorly understood for too long. A focus on adolescence, proximal risk factors, biological acute stress response systems, longitudinal designs, within-person analytic approaches, moderators of the short-term association between stress and suicidal ideation and behaviors, and identification of factors that promote suicide, but not other psychological symptoms, as unique outcomes among youth with multiple risk factors all represent high priority areas for future research.

Yet, it deserves mention that there these suggested research directions should be considered in the context of many other highly salient factors that are beyond the scope of this review. For example, the acute stress response risk model suggested herein should be considered in the context of gender, particularly given adolescent girls’ increased experience of social stress, greater biological and emotional reactivity to interpersonal stress (Rose & Rudolph 2006; Stroud et al. 2017), and emerging data suggesting unique biological factors among females (i.e., circulating reproductive hormones) that may modulate stress response systems (see Eisenlohr-Moul et al. 2018a). Adolescent suicide also must be considered in the context of cultural factors, such as race, ethnicity, and religiosity that are remarkably relevant, but often neglected determinants of suicidal outcomes (Goldston et al. 2008). Our review also did not address a myriad of protective factors that may buffer the effects of risk on adolescents’ suicidal behavior; this remains a critically understudied, yet important direction for research (see Gallagher & Miller 2017). Last, adolescent suicide may be best understood in the context of the macrosystem (Bronfenbrenner 1979) to better understand cultural and political factors that may prove especially relevant to adolescent groups traditionally at risk for suicide (LGBTQ+) and may at
least partially explain generational differences in the rates of adolescent suicide.

The field of suicide research has grown extensively in the past two decades, marked by an increasing number of publications (Franklin et al. 2017), an increased commitment to federal grant funding (Gordon 2016), and even public awareness of suicidal ideation and behaviors as an urgent public health crisis. A developmentally-informed understanding of suicide may reveal mechanisms and processes that are relevant for reducing the frequency of suicidal deaths across the lifespan.
References


Durkheim E. 1897. Suicide: A sociological study. *Paris Alcan*


Gould MS. 1990. Suicide clusters and media exposure.


Summary Points

1. Suicide remains a leading cause of death among adolescents despite decades of research on correlates and risk factors.

2. The developmental period of adolescence creates a unique vulnerability for the emergence of suicidal ideation and behavior as adolescents undergo biological changes and substantial social reorganization. Suicidal crises are often triggered by interpersonal stressors, which increase in frequency and intensity during adolescence.

3. Emerging evidence points to failures in acute stress response systems as a potential mechanism of adolescent suicide.

4. Available data suggests that biological markers of acute stress responses of the autonomic nervous system, hypothalamic-pituitary-adrenal axis, peripheral stress systems (e.g., cytokines), and neural systems may differ among adolescents at risk for suicide.

5. While abnormal acute stress responses may confer risk for psychopathology more generally, we hypothesize that youth who exceed their own typical levels of stress are so remarkably overwhelmed in a suicidal crisis that they turn to suicide as a means of ending distress. Further, we hypothesize that failures in acute stress response systems are particularly likely to precipitate risk for youth exposed to previous suicidal ideation and behaviors, either through exposure to other’s suicidal behavior or through their own past suicidal ideation or behavior.

6. Drawing from a developmental psychopathology perspective, we suggest that the relationship between acute stress response failures and suicidal crisis are transactionally linked. Adolescents’ perceptions of a stressor and their ability to cope are likely altered by acute stress responses failures which in turn lower their threshold for stress tolerance.
in the future.

7. It is unlikely that acute stress response failures explain every type of adolescent suicide risk. However, we believe that across yet to be elucidated phenotypes of suicidal behavior, stress response systems are likely altered.

**Future Issues**

1. Adolescent suicide research must move to focusing on proximal (i.e., hours, minutes, seconds) processes that characterize suicidal crises.

2. Overall, we believe that any future research must consider the unique biological and social changes that characterize adolescence.

3. Leveraging methodologies across multiple units of analysis, such as those suggested by the Research Domain Criteria (RDoC) matrix are likely to sharpen our understanding of the complex behavior of adolescent suicide.

4. We believe the most promising research designs involve combining careful biological assays with rigorous behavioral assessments. An example could include repeated assessments of acute stress responses via laboratory-based visits with ecological momentary assessments of behaviors in between sessions.

5. A crucial step facing future adolescent research is more careful phenotyping of suicidal behavior. We are not the first to call for examining subtypes of behavior, but we believe that it is imperative to move towards a more individualized model of risk rather than treating all suicidal ideation and behavior as the same outcome.
Figure 1. Heuristic model of adolescent suicidal ideation and behavior as a failure of acute biological stress response systems.