Curr Behav Neurosci Rep (2017) 4:79–86
DOI 10.1007/s40473-017-0117-6

CHILD AND DEVELOPMENTAL PSYCHIATRY (K FITZGERALD, SECTION EDITOR)

# Multi-level Analysis of the Functioning of the Neurobiological Threat System in Adolescents: Implications for Suicide and Nonsuicidal Self-Injury

**Melinda Westlund Schreiner**[1] · **Kathryn R. Cullen**[2] · **Bonnie Klimes-Dougan**[1]

Published online: 4 May 2017
© Springer International Publishing AG 2017

**Abstract**
*Purpose of Review* Advancement in knowledge of the neurobiological underpinnings of suicide and nonsuicidal self-injury (NSSI) will require multi-level approaches to understand the typical and atypical developmental processes in systems that are relevant to these aberrant behaviors. Here we focus on the threat system as a prototype, with the goal of integrating research investigating both the central and peripheral arms of this system, as well as the interplay between the brain and the body, during adolescence.
*Recent Findings* An examination of research on the central and peripheral measures of the threat system in typically and atypically developing populations illustrates how the integration of multiple levels of analysis can be optimal in the comprehensive assessment of a system's functioning. Further, this examination of the literature to date highlights important considerations for future work incorporating populations that engage in self-harm.
*Summary* Future adolescent research investigating the neurobiology implicated in suicide and NSSI would benefit from the application of multiple units of analysis that is embedded in a developmental psychopathology perspective.

This article is part of the Topical Collection on *Child and Developmental Psychiatry*

✉ Kathryn R. Cullen
rega0026@umn.edu

[1] Department of Psychology, University of Minnesota, Elliott Hall N218, 75 East River Road, Minneapolis, MN 55455, USA

[2] Department of Psychiatry, University of Minnesota Medical School, F268 West Building, 2450 Riverside Avenue, Minneapolis, MN 55454, USA

**Keywords** Neurobiology · Adolescence · Suicide · Nonsuicidal self-injury · Development · Cortisol · Neuroimaging

## Introduction

Self-harm is defined as "intentional self-poisoning or self-injury [involving tissue damage] irrespective of type of motive or the extent of suicidal intent" [1]. Self-harm may include nonsuicidal self-injury (NSSI) and suicide attempts, the former not involving suicidal intent and the latter involving suicidal intent. Self-harm, a significant problem in adolescence, is overrepresented in those struggling with mental disorders, and may lead to suicide [2–4]. The neurobiology underlying self-harm is poorly understood, and represents an area in urgent need of new research to guide treatment and prevention efforts. Advancement in this knowledge will require a focus on understanding the typical and atypical developmental processes in systems that are relevant to these aberrant behaviors.

With increasing attention being given to neurobiological correlates of psychopathology, research has begun to consider the use of multiple levels of analysis of a system and how they interact with one another. For example, the Research Domain Criteria Project (RDoC), which has been put forward by the National Institutes of Mental Health, promotes research that transcends traditional diagnostic categories and focuses on the various factors that contribute to the development of discrete behaviors [5]. These concepts are foundational to the organizational perspective of developmental psychopathology [6, 7]. Specifically, (a) the emergence of psychopathology is associated with incoherence within and across various biological and psychological systems; (b) early failure to achieve developmental milestones predicts later derailments in functioning; and (c) disruptions in one system earlier in life may later impact other

systems [8•]. Thus, a developmental and integrative perspective allows for a more holistic understanding of the various sequelae that may occur following early neurobiological and psychological insults. Research on self-harm behaviors are well-suited for the application of this approach as they occur across diagnostic categories and likely represent a manifestation of abnormalities in the development of several psychological and biological processes [9]. Investigating self-harm in adolescence is of particular interest as it allows for a better understanding of how disruptions in neurobiological systems may precede the development of disordered behavior. Such research can then lay the foundation for the development of prevention and intervention strategies that target these neurobiological factors and restore developmental trajectories.

The purpose of this paper is to work toward understanding core neurobiological systems of relevance to self-harm. Given available research and its relevance to self-harm, the threat system provides a useful example of how future suicide and NSSI research can examine the interplay of neurobiological measures within a system (or to use RDoC terms, a "domain"). Survival and self-preservation from injury are basic instincts that perpetuate our species. Some of the most challenging life experiences involve threats to self-preservation. Prominent theory [10] suggests that interpersonal threats to the self, including feelings of rejection, alienation, and burdensomeness, in addition to reduced threshold for self-preservation (which may take the form of NSSI), place an individual at high risk for suicide. Thus, the threat system is ideally suited to serve as a prototype for examination of other systems, with the goal of integrating research investigating both the central and peripheral arms of this system, as well as the interplay between the brain and the body, during adolescence.

Examining the interplay between central and peripheral nervous system functioning can provide a more detailed assessment of the threat system. We will first describe each of these levels and the existing literature examining how these different levels of analysis individually relate to adolescent suicide and NSSI. Because no research is currently available on the interplay within this population, we will consider evidence from the small body of developmental research available on the interplay between peripheral and central nervous system functioning and the implications for suicide and NSSI. Finally, we conclude by highlighting important considerations that appear within the existing literature that would be beneficial to future work examining the interplay of these different levels of analysis and the interplay between these levels of analysis for adolescent suicide and NSSI behavior.

## Threat System Functioning: Peripheral and Central Arms

Scientists have begun to appreciate the association between the central (corticolimbic structures and functions) and the peripheral (particularly cortisol) by-products of the neuroendocrine system. Current knowledge suggests that these indices function interdependently. At the corticolimbic level, the organism orchestrates responses to strong emotions or anticipated threat by activating limbic areas, while also recruiting action from prefrontal areas to regulate emotional responses [11]. Efforts to further explicate the interplay between these key neurobiological measures are critical for advancing knowledge about how stressors in our environment promote or interfere with a host of developmental processes [12].

Physiological systems are marshaled when a substantial threat is perceived. In the hypothalamic-pituitary-adrenal (HPA) axis, corticotropin-releasing hormone (CRH) is released by the hypothalamus and triggers a release of adrenocorticotropic hormone (ACTH) from the anterior pituitary. ACTH then stimulates the adrenal cortex to release cortisol. Regulation of this system is then controlled through negative feedback. Cortisol represents the most widely studied measure of the HPA axis, one of the body's chief peripheral threat response systems.

### Peripheral Measurement of the Threat System

Cortisol can be measured in blood or saliva in various contexts, including rest at different parts of the circadian cycle, or during stress conditions. A wealth of research has utilized the Trier Social Stress Test (TSST) [13], a social stress paradigm in which participants complete a speech and arithmetic task in front of an audience. Cortisol is typically measured before and at regular increments following the task. Additionally, other measures at specific times of the day that have been linked to stress sensitivity include the cortisol awakening response (CAR), in which the pattern of increasing HPA activity upon awakening is measured [14], and the diurnal slope across the day (DSL) or at the nadir at bedtime [15]. Some studies have also used the dexamethasone suppression test (DST), in which cortisol is assessed prior to and following the ingestion of dexamethasone. Failure of dexamethasone to suppress cortisol release is then interpreted to reflect HPA axis dysregulation.

Developmentally, the emergence of adolescence is accompanied by heightened arousal of the HPA axis. Basal cortisol levels typically show a pattern of decline across the day and have been found to increase overall with age across the transition to adolescence, as well as with pubertal developmental stage [16]. Reactivity is typically adaptive under conditions of acute threat when the body necessitates heightened resources to adequately respond to a stressor. Cortisol reactivity to stressors appears to increase in adolescence, shows moderate correlation with pubertal development, and in girls, cortisol reactivity has been associated with anxious temperament [16]. Findings from studies examining cortisol levels from protracted stressors and those from acute stressors have different implications in regard to negative effects on the body, such as immune system functioning [17]. When circulating cortisol

remains high (hypercortisolemia), there are a number of associated disruptions including dendritic atrophy [18]. Under some conditions, the presence of chronically high cortisol elevations leads to an allostatic shift, in which the body adjusts itself by suppressing the cortisol response, illustrated by lower diurnal or stress reactive cortisol levels that may represent a mismatch with the environmental context.

## Peripheral Measures of the Stress System: Findings in Suicide and NSSI Research

There is some preliminary evidence suggesting that adolescents with NSSI may fail to garner the appropriate biological resources needed to address a social threat. For example, Kaess and colleagues found that 14 female adolescents with NSSI had a blunted stress response to acute social stress compared to 14 healthy controls [19]. This was recently replicated in a study that examined blood cortisol levels in response to a social stressor in 21 19-year-old females with NSSI [20]. Low levels of blood cortisol were also inversely related to high ideation and retrospective self-injury among adolescents with depression following a DST [21]. However, the methodology in this study does not allow for differentiating between the possible explanations of lower tonic cortisol production and the impaired negative feedback system functioning. While these patterns of threat activation and regulation may be functional within the environmental contexts in which these alterations arise, these alterations may also represent significant developmental liabilities.

## Central Measures of the Stress System

The advance of neuroimaging has opened new doors for understanding brain development and brain functioning in the context of psychopathology such as suicide and self-harm behaviors. Structural MRI provides information regarding the volume or thickness of particular brain regions. Functional MRI (fMRI) data can be collected at rest or during a task, and can provide information about brain activation and functional connectivity between different brain regions. Another index of brain functioning is diffusion weighted imaging (dMRI), which provides information about the structural integrity of white matter. These measures allow us to understand more about the efficiency of the transmission of neural signals within and between regions of the brain.

Developmentally, gray matter volumes peak during preadolescence, followed by a decrease throughout adolescence; in contrast, white matter increases linearly between the ages of 4 and 20 years [22]. The continuing maturation of gray and white matters during adolescence may implicate this period as a time of a greater predisposition to the development of abnormal brain structure and function [22]. Given that the HPA axis is set in motion by the limbic system and is then regulated by negative feedback with cortical regions, studies incorporating peripheral measures with more central indices of corticolimbic structure and/or function are of primary interest.

## Central Measures of the Stress System: Findings in Suicide and NSSI Research

Prior studies examining corticolimbic structure in populations with a history of self-harm have found evidence of larger amygdala and pituitary volumes, as well as compromised white and gray matter structures within frontal regulatory regions of the brain [23–25]. Greater pituitary and amygdala volumes may represent a neuroimaging biomarker of facilitated stress response in people with a history of suicide attempts and NSSI. Further, compromised structure of prefrontal regions may potentially reflect limited capacity to downregulate limbic activation and HPA arousal.

In line with structural findings, those with suicide and NSSI behavior have shown greater amygdala activation in response to both negative and neutral stimuli (suggesting potential generalization of stress response) [26]. Further, in response to a script describing the reaction to a self-injury event, patients with borderline personality disorder (BPD) and a history of self-injury showed lower orbitofrontal and midcingulate activation compared to controls, but greater dorsolateral prefrontal cortex activation compared to controls [27]. Diminished orbitofrontal activation may represent impaired inhibition of the emotional reactions; diminished midcingulate activation may reflect active monitoring deficits (leading to enhanced emotional involvement), while enhanced dorsolateral prefrontal cortex may indicate a dysfunction in response selection in the context of negative emotion. Thus, this pattern of dysregulation may represent neurobiological markers relevant to the complex psychological processes leading to and maintaining self-harm behaviors.

Neuroimaging studies examining patients with suicidal or NSSI behavior do not always show anomalous patterns of neural circuitry. In a study by Pan and colleagues, healthy controls were compared to depressed adolescents with and without suicidal histories while completing a go-no-go task during functional imaging. Those with major depressive disorder (MDD) and suicide attempts did not show any significant differences in connectivity when compared to healthy controls. Instead, those with MDD and no suicide attempts showed increased activity in the right anterior cingulate cortex (ACC) compared to those with suicide attempts and greater activity in the left insula during these times compared to healthy controls [28]. The authors suggest that due to the role of the insula in internal state monitoring and autonomic function monitoring, those with MDD and no suicide attempts may have abnormally elevated levels of these functions, particularly internal state monitoring. Further, greater activation

of the right ACC among those with MDD and no suicide attempts compared to those with suicide attempts may be a reflection of increased recruitment of this region to facilitate accuracy during response inhibition. This study highlights the importance of applying a developmental perspective to this research, ideally using longitudinal designs, to explore the possible role of compensatory processes that may develop over time in the context of chronic self-harm behaviors.

## Interplay of Central and Peripheral Measures of the Stress System

We now consider how the existing developmental literature on the interplay across central and peripheral systems may inform future research on self-harm. Some efforts to examine the interplay between the corticolimbic neurocircuitry and the neuroendocrine system are underway. Although this work is typically with healthy or depressed adults, it may provide some broad evidence of relevant patterns for self-harming adolescents. Examples within the adult literature include links between brain volume of related corticolimbic regions and basal HPA axis functioning [29] and also between brain functioning during a fear conditioning paradigm and HPA reactivity [30]. In particular, cortisol reactivity was positively associated with amygdala and hippocampal activity and negatively associated with the ventromedial prefrontal cortex activity during the completion of the task. In addition to considering more widespread associations, others have noted that those who respond to a stress paradigm by exhibiting elevated salivary cortisol levels show differences in brain functioning in expected corticolimbic regions as compared to those who do not respond to a stress paradigm [31]. Considering the existing literature on the interplay of peripheral and central nervous systems in typically and atypically developing adolescent populations (as detailed below) provides a framework for future research probing the biological mechanisms that underlie self-harm.

### Normative Development

To date, there have been a few studies that have used an integrative approach to examine the interplay between the HPA axis and the neuroimaging measures within the context of normative adolescent development. In regard to brain structure, Kaess and colleagues examined the development of pituitary gland volume and HPA reactivity via CAR and DSL in a sample of 19 adolescent females and 30 adolescent males. Because of the involvement of the pituitary gland in the hormonal cascade of the HPA axis, studies examining the volume of this region may provide insight into the relationship between structure and function. Within the group of males, pituitary gland volume at the age of 12 years old was positively associated with HPA reactivity as measured by the CAR and DSL at 15–16 years old [32]. No such association was found for females, highlighting the importance of considering differing developmental trajectories between males and females. However, it should be noted that the small sample size for females in this study ($n = 19$) might not have provided enough power to detect significant effects. Nonetheless, the importance of investigating sex differences is supported with regard to suicide as adolescent females are more likely to attempt suicide, while males are more likely to die by suicide [33].

In regard to associations between fMRI and HPA activity, a study of 24 adolescent males classified as young (12–13 years old) or old (16–17 years old) examined the relationship between pre- and post-MRI cortisol levels and brain activation during a gambling task [34••]. Overall, higher cortisol was associated with decreased brain activation, with location of findings dependent on age. There was a negative association between cortisol and activation of the anterior and posterior cingulate cortices among young adolescents and a negative association between cortisol and activation of the inferior parietal and superior frontal cortices in older adolescents. Broadly, these results suggest that greater activation of frontal regulatory regions corresponds with lower levels of cortisol in adolescents. It is possible that this relationship is impaired among those who engage in suicidal and NSSI behavior. As reviewed previously, studies of self-harm suggest both anomalous corticolimbic and HPA functioning when examined separately. Further research is needed to understand how these two indices relate to one another in self-harm.

In a multi-modal study of 33 children and adolescents aged 7–15 years, cortisol response to an acute stressor (the TSST-C), resting-state functional connectivity (RSFC) of the hippocampus, and self-reported anxiety before and after the MRI scan were examined. Greater cortisol in response to the acute stressor was associated with greater RSFC between the hippocampus and the regions of the default mode network [35], a network of brain regions that are more active at rest [36] and believed to mediate emotional cognition, introspection, and autobiographical memory [37]. Similarly, a study of 49 children aged 9–15 years showed that greater cortisol reactivity in response to a social stress test was associated with RSFC between the subgenual anterior cingulate cortex and the salience network [38], which is a network of brain regions associated with interoceptive and emotional awareness [39]. Taken together, these studies suggest that children and adolescents with a predisposition for assigning higher self-relevance in connection to memory and affective experience may respond to acute stressors more intensely. It is possible that these cortisol-RSFC relationships represent a continuum in which a stronger (or perhaps even weaker) relationship may set the stage for the development of maladaptive coping strategies such as suicidal and NSSI behavior.

## Stress and Trauma

Aside from research examining interplay of central and peripheral arms of the stress system in the context of normative development, another relatively well-studied area applicable to the present review consists of research incorporating early life stress and trauma. The onset of adolescent psychopathology, including suicide and NSSI, is often preceded by substantial environmental stressors. Studying samples of adolescents who are chronically stressed, but have not yet developed psychopathology, may provide important information about the temporal relationship between the system dysregulation within different ways of measurement and the development of psychiatric disorders. Further, evidence indicates that stressors that occur very early in life can impact HPA reactivity and brain connectivity. As reviewed by Heim, Meinlschmidt, and Nemeroff, early life stressors can have a substantial impact on neurodevelopment and may serve as a prime for later psychopathology [40••], which may then be a precursor for later suicide or NSSI. Available research targets populations with early life stressors, including economic hardships as reflected by low socioeconomic status (SES) as well as more discrete experiences such as maltreatment. Sheridan and colleagues examined parental SES, prefrontal cortex activation, and cortisol response pre- and post-MRI. Lower percent change in cortisol pre- vs. post-MRI was associated with lower SES and greater activation of the right middle frontal gyrus during a learning task aimed to measure executive functioning [41].

Regarding experiences earlier in life, white matter organization and cortisol were examined in a sample of 25 children aged 8–14 years who experienced maltreatment before the age of three. Puetz and colleagues found that these children had reduced global white matter connectivity, which was associated with blunted CAR and increased internalizing and externalizing symptoms, compared to 24 healthy control children aged 7–13 years [42].

Extending further into development, 23 adolescents, aged 14–17 years from high stress environments (e.g., poverty and maltreatment), completed a child version of the TSST and were scanned while participating in a task that involved processing emotional faces [43]. A greater increase in cortisol from pre- to post-TSST was associated with less left hippocampal activation during the processing of fearful faces [43]. As highlighted by the authors, the hippocampus plays an important role in the negative feedback loop of the HPA axis due to its inhibitory control of the hypothalamus [44]. Further, research has implicated a deleterious effect of chronic stress on the hippocampus, such as the study described previously [45]. The results of Liu and colleagues suggest that adolescents in chronic stress environments may have deficits in appropriately downregulating cortisol release, which may relate to failures in effectively coping with challenging situations.

Longitudinal methodologies considering the interplay between levels of analysis provide possible temporal explanations for the development of psychopathology. Carrion, Weems, and Reiss examined the relationship between posttraumatic stress disorder symptoms (PTSD), cortisol, and hippocampal volume in a sample of 15 8- to 14-year-old children. Data was collected at baseline and again after 12–18 months. Greater severity of PTSD symptoms and higher cortisol levels at baseline significantly predicted a reduction in hippocampal volume 12–18 months later [45]. Additionally, Burghy et al. evaluated 57 participants who completed salivary basal cortisol collection when they were approximately 4.5 years of age and a structural MRI, resting-state fMRI, and a self-report assessment of psychiatric symptoms at approximately 18 years of age. Although there were no significant findings with the males in the sample, females who experienced stress in infancy had heightened cortisol at the age of 4.5 years. In turn, heightened cortisol at 4.5 years predicted negative frontal-limbic resting-state functional connectivity (specifically, amygdala-ventromedial prefrontal cortex) at age 18 years. Further, negative functional connectivity between amygdala and ventromedial prefrontal cortex was associated with self-reported levels of anxiety at 18 [46]. Together, these findings provide important possibilities regarding the timeline of the disruption that occurs within the corticolimbic system. Although causal conclusions are not yet warranted, the extant evidence provides a basis for the hypothesis that early life stress may lead to hyperreactivity of the HPA axis in childhood, which then impacts hippocampal activation and corticolimbic functional connectivity [45, 46].

A potential confound of investigating the influence of environmental stressors on neurobiological development is the presence of sex differences. Indeed, studies have suggested that in regard to neurodevelopment, females appear to be more susceptible to outside influences compared to males [47]. This is illustrated in the aforementioned studies, particularly that of Burghy and colleagues, which found significant relationships only among females. Although this suggests the importance of examining the role of sex on these interactions, existing research in this area is frequently limited to small sample sizes, thus highlighting the importance of further research in this area.

## Depression

Interplay of neurobiological measures in the context of adolescent depression may lend important insights regarding how these relationships manifest in suicide and NSSI behavior, particularly since both suicide and NSSI are highly related to depression [48, 49]. LeMoult and colleagues investigated the relationship between CAR and activation of the ventral striatum during a reward task in pre- and post-menarcheal adolescent females at high risk for depression (due to presence of

maternal depression). Among the post-menarcheal females, CAR was strongly associated with ventral striatum activity during reward anticipation [50••]. Because there were no differences between the pre- and post-menarcheal females in the linkage between CAR and ventral striatum activity during neutral trials, the authors suggest that post-menarcheal adolescents show greater reward-related responsivity to affective stimuli across both stress hormone and neural substrate for reward processing.

Thus far, only one study has examined the interplay between cortisol and neural structures and functioning in adolescent depression. In a sample of 52 adolescents aged 12–10 years with major depressive disorder (16 with current antidepressant medication) and 27 age- and gender-matched healthy controls, Klimes-Dougan et al. investigated the relationship between cortisol response in two different contexts (TSST and pre-post MRI) and amygdala volume and amygdala activation in response to an emotion face-matching task [51••]. In regard to the relationship between TSST cortisol response and amygdala volume, there was a significant interaction in which those with MDD showed a positive association while healthy controls showed a negative association. There was a positive correlation between TSST cortisol levels and amygdala activation, but the relationship was similar for both the depressed and healthy adolescents. Together, the research on those at risk for and those diagnosed with depression shows evidence of corresponding activation of the HPA axis with striatal and limbic brain regions. But, the implications of this work as it pertains to adolescents who engage in self-harm remain elusive. It is possible that the pattern of HPA axis hypoarousal that characterizes adolescents with NSSI would show less correspondence across systems. As such, the interplay patterns may serve to differentiate depressed adolescents who do from those who do not engage in NSSI.

## Summary and Conclusion

There is a need to understand the biological underpinnings of typical and atypical developmental processes if we intend to advance our understanding of suicide and nonsuicidal self-injury in adolescents. There is a small body of work that considers these systems separately, possibly suggesting a possible incongruence across systems—with hyperarousal of central, but hypoarousal of peripheral indices of threat response. However, an integrative approach, considering congruence or incongruence in functioning across systems, has yet to be pursued in suicide or NSSI research. The existing research investigating the interplay between central and peripheral measures of the stress system in adolescents is limited to work that falls within the context of normative development, early stress and trauma, and depression. Nevertheless, this existing research on the interplay across systems may serve to highlight important considerations for future work.

One important theme that emerges is that research findings on the interplay between central and peripheral arms of the threat system need to be placed within the context of normative development. As indicated by Keulers and colleagues, findings regarding the interplay between cortisol and corticolimbic structure and function may differ depending on age, even within the adolescent period [34••]. Additionally, longitudinal designs that incorporate high-risk samples are necessary to elucidate the temporal relationship of events across development (i.e., does disruption in cortisol precede disruption in corticolimbic structure or function, and at what time in the unfolding of these changes does risk for self-harm behaviors begin?). Early stress and trauma may predispose individuals to the development of suicide, NSSI, and other forms of psychopathology [41], implicating neural and hormonal developmental processes. [40••, 41, 42, 43, 45, 46].

Expanding the examination of dynamic neural systems across development implicated in suicide and NSSI is needed. Longitudinal studies of at-risk children have demonstrated developmental cascades for psychopathology [52, 53], where problems in one system emerge as a result of cumulative effects in another system. Thus, a deficit occurring early in development can give rise to a cascade of more complex deficits as different brain regions mature and interact over time. While the focus here has been primarily on threat and to a lesser extent regulatory control, social processes are only more recently being examined [clinicaltrials.gov NCT02947308]. For example, one key intrapersonal factor may be the manner in which participants with self-harm struggle with handling challenges to the self, implicating disrupted self-referential processing. Reference of self may occur in part of the medial cortical network (MCN) involving the rostral and posterior cingulate cortex and precuneus [54]. This network has not yet been directly examined in self-injury, but warrants more attention in the future, particularly as interpersonal difficulties are common within this population [55].

Relatedly, sex differences, gender differences, and pubertal development are key considerations that require full consideration in this line of work. In two of the reviewed studies, significant findings only existed after looking at males and females separately [32, 46]. Further, findings from other studies might be driven by overrepresentation of one of the sexes [51••]. In regard to research examining suicide and NSSI, sex differences are important to consider as rates of suicide attempts, suicide completions, and NSSI differ significantly between males and females, as do brain and HPA axis functioning [22, 33, 47, 56, 57]. Thus, a critical next step is to understand neurobiological factors to account for these critical factors, as they are likely to have an influence on neurobiological interplay.

Given the recent surge in interest regarding neurobiological underpinnings of pathological thoughts and behavior, the

existing research climate is well primed for furthering our understanding of suicide and NSSI. Specifically, the field would benefit greatly by considering the interplay of multiple levels of a system to provide a more holistic understanding of the neurobiology. Although the present review focused on the application of interplay between central and peripheral arms of the stress system, future work is needed to examine interplay across other systems relevant to suicide and NSSI, such as those involving interpersonal functioning, pain, and reward. Further, longitudinal research across development is necessary to understand the temporal relationship of these measures. This line of research has a promise to ultimately help identify those at highest risk early in development and employ neurobiologically informed interventions that target potential anomalies to prevent suicide and NSSI.

**Compliance with Ethical Standards**

**Conflict of Interest** Melinda Westlund Schreiner, Dr. Kathryn R. Cullen, and Dr. Bonnie Klimes-Dougan declare that they have no conflicts of interest.

**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


1. Hawton K, Saunders K, Topiwala A, Haw C. Psychiatric disorders in patients presenting to hospital following self-harm: a systematic review. J Affect Disord Elsevier. 2013;151:821–30.
2. Tang J, Yu Y, Wu Y, Du Y, Ma Y, Zhu H, et al. Association between non-suicidal self-injuries and suicide attempts in Chinese adolescents and college students: a cross-section study. PLoS One. 2011;6:e17977.
3. Horwitz AG, Czyz EK, King CA. Predicting future suicide attempts among adolescent and emerging adult psychiatric emergency patients. J Clin Child Adolesc Psychol. 2014:1–11.
4. Victor SE, Klonsky ED. Correlates of suicide attempts among self-injurers: a meta-analysis. Clin Psychol Rev. 2014;34:282–97.
5. Sanislow CA, Pine DS, Quinn KJ, Kozak MJ, Garvey MA, Heinssen RK, et al. Developing constructs for psychopathology research: research domain criteria. J Abnorm Psychol. 2010;119:631–9.
6. Cicchetti D, Rogosch FA. A developmental psychopathology perspective on adolescence. J Consult Clin Psychol. 2002;70:6–20.
7. Cicchetti D, Toth SL. The development of depression in children and adolescents. Am Psychol. 1998;53:221–41.
8.• Casey BJ, Oliveri ME, Insel T. A neurodevelopmental perspective on the research domain criteria (RDoC) framework. Biol Psychiatry. 2014;76:350–3. **Highlights the importance of emphasizing a developmental framework when investigating the neurobiology of behavior.**
9. Westlund Schreiner M, Klimes-Dougan B, Begnel ED, Cullen KR. Conceptualizing the neurobiology of non-suicidal self-injury from the perspective of the Research Domain Criteria Project. Neurosci Biobehav Rev. 2015;57:381–91.
10. Joiner TE. 2005 Why people die by suicide. Cambridge, MA: Harvard University Press.
11. Stein JL, Wiedholz LM, Bassett DS, Weinberger DR, Zink CF, Mattay VS, et al. A validated network of effective amygdala connectivity. NeuroImage. 2007;36:736–45.
12. Lupien SJ, McEwen BS, Gunnar MR, Heim C. Effects of stress throughout the lifespan on the brain, behaviour and cognition. Nat Rev Neurosci Nature Publishing Group. 2009;10:434–45.
13. Kirschbaum C, Pirke KM, Hellhammer DH. The "Trier Social Stress Test"—a tool for investigating psychobiological stress responses in a laboratory setting. Neuropsychobiology. 1993;28:76–81.
14. Pruessner JC, Wolf OT, Hellhammer DH, Buske-Kirschbaum A, von Auer K, Jobst S, et al. Free cortisol levels after awakening: a reliable biological marker for the assessment of adrenocortical activity. Life Sci. 1997;61:2539–49.
15. Adam EK, Kumari M. Assessing salivary cortisol in large-scale, epidemiological research. Psychoneuroendocrinology. 2009;34:1423–36.
16. Gunnar MR, Wewerka S, Frenn K, Long JD, Griggs C. Developmental changes in hypothalamus–pituitary–adrenal activity over the transition to adolescence: normative changes and associations with puberty. Dev Psychopathol. 2009;21:69.
17. Sapolsky R. 1994 Why zebras don't get ulcers. New York, NY: WH Freeman.
18. Juster R-P, McEwen BS, Lupien SJ. Allostatic load biomarkers of chronic stress and impact on health and cognition. Neurosci Biobehav Rev. 2010;35:2–16.
19. Kaess M, Hille M, Parzer P, Maser-Gluth C, Resch F, Brunner R. Alterations in the neuroendocrinological stress response to acute psychosocial stress in adolescents engaging in nonsuicidal self-injury. Psychoneuroendocrinology. 2012;37:157–61.
20. Plener PL, Zohsel K, Hohm E, Buchmann AF, Banaschewski T, Zimmermann US, et al. Lower cortisol level in response to a psychosocial stressor in young females with self-harm. Psychoneuroendocrinology. 2017;76:84–7.
21. Beauchaine TP, Crowell SE, Hsiao RC. Post-dexamethasone cortisol, self-inflicted injury, and suicidal ideation among depressed adolescent girls. J Abnorm Child Psychol. 2015;43:619–32.
22. Giedd JN, Blumenthal J, Jeffries NO, Castellanos FX, Liu H, Zijdenbos A, et al. Brain development during childhood and adolescence: a longitudinal MRI study. Nat Neurosci. 1999;2:861–3.
23. Monkul ES, Hatch JP, Nicoletti MA, Spence S, Brambilla P, LT LA, et al. Fronto-limbic brain structures in suicidal and non-suicidal female patients with major depressive disorder. Mol Psychiatry. 2007;12:360–6.
24. Grant JE, Correia S, Brennan-Krohn T, Malloy PF, Laidlaw DH, Schulz SC. Frontal white matter integrity in borderline personality disorder with self-injurious behavior. J Neuropsychiatry Clin Neurosci. 2007;19:383–90.
25. Jovev M, Garner B, Phillips L, Velakoulis D, Wood SJ, Jackson HJ, et al. An MRI study of pituitary volume and parasuicidal behavior in teenagers with first-presentation borderline personality disorder. Psychiatry Res. 2008;162:273–7.
26. Niedtfeld I, Schulze L, Kirsch P, Herpertz SC, Bohus M, Schmahl C. Affect regulation and pain in borderline personality disorder: a possible link to the understanding of self-injury. Biol Psychiatry. 2010;68:383–91.
27. Kraus A, Valerius G, Seifritz E, Ruf M, Bremner JD, Bohus M, et al. Script-driven imagery of self-injurious behavior in patients with borderline personality disorder: a pilot FMRI study. Acta Psychiatr Scand. 2010;121:41–51.

28. Pan LA, Batezati-Alves SC, Almeida JRC, Segreti A, Akkal D, Hassel S, et al. Dissociable patterns of neural activity during response inhibition in depressed adolescents with and without suicidal behavior. J Am Acad Child Adolesc Psychiatry NIH Public Access. 2011;50:602–11. **e3**
29. Axelson DA, Doraiswamy PM, McDonald WM, Boyko OB, Tupler LA, Patterson LJ, et al. Hypercortisolemia and hippocampal changes in depression. Psychiatry Res. 1993;47:163–73.
30. Root JC, Tuescher O, Cunningham-Bussel A, Pan H, Epstein J, Altemus M, et al. Frontolimbic function and cortisol reactivity in response to emotional stimuli. Neuroreport. 2009;20:429–34.
31. Pruessner JC, Dedovic K, Pruessner M, Lord C, Buss C, Collins L, et al. Stress regulation in the central nervous system: evidence from structural and functional neuroimaging studies in human populations—2008 Curt Richter Award Winner. Psychoneuroendocrinology. 2010;35:179–91.
32. Kaess M, Simmons JG, Whittle S, Jovev M, Chanen AM, Yücel M, et al. Sex-specific prediction of hypothalamic-pituitary-adrenal axis activity by pituitary volume during adolescence: a longitudinal study from 12 to 17 years of age. Psychoneuroendocrinology. 2013;38:2694–704.
33. CDC. WISQARS (Web-based Injury Statistics Query and Reporting System)|Injury Center|CDC.
34.•• Keulers EHH, Stiers P, Nicolson NA, Jolles J. The association between cortisol and the BOLD response in male adolescents undergoing fMRI. Brain Res. 2015;1598:1–11. **Study that, along with others, highlights how interplay findings may differ between the sexes**
35. Thomason ME, Tocco MA, Quednau KA, Bedway AR, Carré JM. Idle behaviors of the hippocampus reflect endogenous cortisol levels in youth. J Am Acad Child Adolesc Psychiatry. 2013;52:642–652.e1.
36. Raichle ME, Macleod AM, Snyder AZ, Powerst NJ, Gusnard DA, Shulman GL. A default mode of brain function. Proc Natl Acad Sci. 2001;98:676–82.
37. Laird AR, Eickhoff SB, Li K, Robin DA, Glahn DC, Fox PT. Investigating the functional heterogeneity of the default mode network using coordinate-based meta-analytic modeling. J Neurosci. 2009;29:14496–505.
38. Thomason ME, Hamilton JP, Gotlib IH. Stress-induced activation of the HPA axis predicts connectivity between subgenual cingulate and salience network during rest in adolescents. J Child Psychol Psychiatry. 2011;52:1026–34.
39. Seeley WW, Menon V, Schatzberg AF, Keller J, Glover GH, Kenna H, et al. Dissociable intrinsic connectivity networks for salience processing and executive control. J Neurosci. 2007;27:2349–56.
40.•• Heim C, Nemeroff CB. Neurobiology of early life stress: clinical studies. Semin Clin Neuropsychiatry. 2002;7:147–59. **Study examining the subsequent effects of early life maltreatment on the interplay between cortisol and corticolimbic structures**
41. Sheridan MA, Sarsour K, Jutte D, D'Esposito M, Boyce WT. The impact of social disparity on prefrontal function in childhood. Zhan W, editor. PLoS One Lawrence Erlbaum Associates Publishers; 2012;7:e35744.
42. Puetz VB, Parker D, Kohn N, Dahmen B, Verma R, Konrad K. Altered brain network integrity after childhood maltreatment: a structural connectomic DTI-study. Hum Brain Mapp. 2017;38:855–68.
43. Liu J, Chaplin TM, Wang F, Sinha R, Mayes LC, Blumberg HP. Stress reactivity and corticolimbic response to emotional faces in adolescents. J Am Acad Child Adolesc Psychiatry. 2012;51:304–12.
44. Herman JP, Figueiredo H, Mueller NK, Ulrich-Lai Y, Ostrander MM, Choi DC, et al. Central mechanisms of stress integration: hierarchical circuitry controlling hypothalamo-pituitary-adrenocortical responsiveness. Front Neuroendocrinol. 2003;24:151–80.
45. Carrion VG, Weems CF, Reiss AL. Stress predicts brain changes in children: a pilot longitudinal study on youth stress, posttraumatic stress disorder, and the hippocampus. Pediatrics. 2007;119:509–16.
46. Burghy CA, Stodola DE, Ruttle PL, Molloy EK, Armstrong JM, Oler JA, et al. Developmental pathways to amygdala-prefrontal function and internalizing symptoms in adolescence. Nat Neurosci. 2012;15:1736–41.
47. Oldehinkel AJ, Bouma EMC. Sensitivity to the depressogenic effect of stress and HPA-axis reactivity in adolescence: a review of gender differences. Neurosci Biobehav Rev. 2011;35:1757–70.
48. Hintikka J, Tolmunen T, Rissanen M-L, Honkalampi K, Kylmä J, Laukkanen E. Mental disorders in self-cutting adolescents. J Adolesc Health. 2009;44:464–7.
49. Kessler RC, Avenevoli S, Ries MK. Mood disorders in children and adolescents: an epidemiologic perspective. Biol Psychiatry. 2001;49:1002–14.
50.•• LeMoult J, Colich NL, Sherdell L, Hamilton JP, Gotlib IH. Influence of menarche on the relation between diurnal cortisol production and ventral striatum activity during reward anticipation. Soc Cogn Affect Neurosci. 2015;10:1244–50. **Study highlighting how pubertal status may affect the interplay between measures. Also, this study demonstrates the increased sensitivity among post-menarcheal females to affective stimuli**
51.•• Klimes-Dougan B, Eberly LE, Westlund Schreiner M, Kurkiewicz P, Houri A, Schlesinger A, et al. Multilevel assessment of the neurobiological threat system in depressed adolescents: interplay between the limbic system and hypothalamic–pituitary–adrenal axis. Dev Psychopathol. 2014;26:1321–35. **Study showing how adolescents with and without depression show opposite patterns of interplay between neurobiological measures**
52. Klimes-Dougan B, Long JD, Lee C-YS, Ronsaville DS, Gold PW, Martinez PE. Continuity and cascade in offspring of bipolar parents: a longitudinal study of externalizing, internalizing, and thought problems. Dev Psychopathol. 2010;22:849–66.
53. Masten AS, Cicchetti D. Developmental cascades. Dev Psychopathol. 2010;22:491–5.
54. Gusnard DA, Akbudak E, Shulman GL, Raichle ME. Medial prefrontal cortex and self-referential mental activity: relation to a default mode of brain function. Proc Natl Acad Sci U S A. 2001;98:4259–64.
55. McMahon EM, Reulbach U, Keeley H, Perry IJ, Arensman E. Bullying victimisation, self harm and associated factors in Irish adolescent boys. Soc Sci Med. 2010;71:1300–7.
56. Andrews T, Martin G, Hasking P, Page A. Predictors of onset for non-suicidal self-injury within a school-based sample of adolescents. Prev Sci. 2014;15:850–9.
57. Zetterqvist M, Lundh L-G, Dahlström O, Svedin CG. Prevalence and function of non-suicidal self-injury (NSSI) in a community sample of adolescents, using suggested DSM-5 criteria for a potential NSSI disorder. J Abnorm Child Psychol. 2013;41:759–73.