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Post-Dexamethasone Cortisol, Self-Inflicted Injury, and Suicidal Ideation Among Depressed Adolescent Girls

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Abstract Although the dexamethasone suppression test (DST) has limited use as a biomarker of depression given inadequate sensitivity and specificity, it marks prospective risk for suicide among adults. However, few studies have examined associations between the DST, suicidal ideation, and self-inflicted injury (SII) among adolescents, even though SII is the single best predictor of eventual suicide. We evaluated the DST as a correlate of suicidal ideation and retrospective reports of self-inflicted injury (SII) among adolescent girls, ages 13–17, with histories of depression (n=28) or depression and self-harm (n=29). Lower post-DST cortisol was associated with suicidal ideation and SII, over-and-above parent-reports and combined parent-/self-reports of internalizing and externalizing behavior. These findings are consistent with recent acquired capacity models of stress-related psychopathology in which hypothalamic-pituitary adrenal (HPA) axis function is altered through epigenetic/allostatic mechanisms among vulnerable individuals who incur adversity early in life.

Keywords Depression · Self-injury · HPA axis · Dexamethasone · Cortisol · Suicidal ideation

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Self-inflicted injury (SII), including suicide attempts and nonsuicidal self-harm (see Crowell et al. 2009; Nock 2010), portends a plethora of adverse outcomes among affected adolescents, including social problems, academic underachievement, poor psychological adjustment, and vulnerability to completed suicide (Crowell et al. 2014; Nock 2010). Although it is difficult to obtain accurate prevalence estimates of SII and related behaviors, rates of self-injury have almost certainly increased over the past two decades, especially among adolescent girls (Center for Disease Control [CDC] 2009; Nock 2008). Even in community samples, up to 45 % of adolescents have engaged in some form of self-harm (Lloyd-Richardson et al. 2007). Moreover, over 400,000 individuals in the US receive medical attention for self-injury each year (CDC 2006). Given the high level of functional impairment associated with SII, and vulnerability it confers to eventual suicide (Klonsky et al. 2013), it is recognized as an urgent public health problem.

In general, prevention and treatment of psychiatric disorders improves with greater understanding of etiology (Beauchaine et al. 2008; Preskorn and Baker 2002). However, very little is known about neurobiological vulnerabilities to SII (see Derbidge and Beauchaine 2014). In this paper, we focus on dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis, which has long been implicated in the pathophysiology of anxiety and depression across the lifespan (Dietrich et al. 2013; Extein et al. 1982; Heim et al. 2008; Knorr et al. 2010; Pfeffer et al. 1991), and in vulnerability to suicide among adults (e.g., Jokinen and Nordstrom 2009; Coryell and Schlesser 2008). To date, however, very few studies have evaluated HPA axis function as a correlate of adolescent suicide attempts or SII. This is a potentially important oversight given that (1) most adolescents who engage in SII and suicide attempts report high levels of depression (see e.g., Crowell et al. 2012), (2) HPA axis dysfunction prospectively predicts suicidal behaviors among adults, as described

in detail below (Jokinen and Nordstrom 2009; Coryell and Schlesser 2008), and (3) acquired capacity models implicate altered stress responding in the development of suicide and related behaviors (Joiner 2005; Joiner et al. 2009).

HPA Axis Function and Depression

Although affective disorders, which are almost always experienced by adolescents who engage in self-harm (see e.g., Crowell et al. 2005) arise from heterogeneous causes (e.g., Klein et al. 2013), many depressed children, adolescents, and adults exhibit dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis (e.g., Dietrich et al. 2013; Extein et al. 1982; Heim et al. 2008; Pfeffer et al. 1991; Knorr et al. 2010), a major component of the human stress response system. Historically, HPA axis dysregulation has been assessed in several ways, including assays of salivary cortisol, both at rest and following psychological stress; corticotropin-releasing hormone (CRH) infusion tests; and the dexamethasone suppression test (DST). These methods evaluate different aspects of HPA axis function (e.g., tonic cortisol production, integrity of negative feedback), and are not equally efficient biomarkers of depression. In a recent meta-analysis comparing the three approaches across 34 child and adolescent samples (N=2258), the global standardized mean effect size for the DST between depressed and non-depressed youth (0.57) was almost three times larger than the mean effect size (0.20) for basal cortisol (Lopez-Duran et al. 2009). Furthermore, CRH infusion did not discriminate depressed from non-depressed groups.

Even though the DST is a more efficient biomarker of depression than either basal cortisol or CRH infusion, a medium effect size does not confer adequate sensitivity or specificity to render the test useful for diagnostic purposes (Casat and Powell 1988; Arana et al. 1985), especially if one assumes that all depressions are etiologically homogenous. However, depression is not a homogeneous construct, and the DST is much more effective in identifying those who suffer from melancholic depression (Arana et al. 1985; Rush et al. 1996), and those with high-risk glucocorticoid receptor polymorphisms (Ruiz et al. 2001). Such findings suggest that HPA axis dysfunction may be associated more specifically with endogenous forms of depression, which portend greater risk of eventual suicide than other forms of depression, especially among women (e.g., Thompson 2012).

The DST and Suicide Risk

As might be expected given the findings outlined above, the DST also identifies depressed inpatients who have attempted suicide (Jokinen and Nordstrom 2009), and psychiatric inpatients who are at heightened prospective risk for suicide (Coryell and Schlesser 2008). In fact, depressed inpatient adults who are DST non-suppressors are at 10-fold risk of completed suicide (26.8 %) at 15-year follow-up compared with those who are DST suppressors (2.9 %). Such prospective prediction of an extremely important clinical outcome suggests that use of the DST as a biomarker of suicide risk might be expanded among depressed populations in efforts to prevent eventual mortality (see Beauchaine et al. 2008).

Importantly, results from studies of HPA axis function among depressed children and adolescents are often inconsistent with results obtained from depressed adults, who typically exhibit *hyper*cortisolaemia (Lopez-Duran et al. 2009). This is indicated by both non-suppression of cortisol following administration of dexamethasone (e.g., Caroll et al. 1976; Arana et al. 1985), and greater cortisol levels following recovery from psychological stress (e.g., Burkea et al. 2005). In contrast, *hypo*cortisolaemia is often observed among children who are vulnerable to depression, especially those who have been maltreated or otherwise traumatized (e.g., Gunnar and Vazquez 2001; Wikgren et al. 2012; see also Van Zomeren-Dohm et al. 2014).

Child abuse in particular alters gene expression in glucocorticoid receptors through epigenetic mechanisms (Klengel et al. 2013; McGowan et al. 2009), which in turn alters HPA axis function and may confer vulnerability to depression and suicide (see Doom and Gunnar 2013). Although we did not assess child abuse in the current sample, it is important to note that among depressed, self-injuring adolescent girls—a growing demographic in the US (see Nock et al. 2013)—and among those with borderline personality disorder (BPD), many of whom also self-injure, rates of child maltreatment and child abuse are exceedingly high (e.g., Maniglio 2011; Norden et al. 1995; see also Beauchaine et al. 2009; Yates 2009). Allostatic alterations in locus coeruleus-norepinephrine system function have also been linked to child maltreatment and sexual abuse (e.g., De Bellis et al. 1999), and to anxiety disorders, depression, and PTSD (see Beauchaine et al. 2011). Importantly, LC-NE responding modulates HPA axis function (Morilak 2007). Unaccounted for child abuse or self-inflicted injury (SII) in models linking HPA axis function to clinical outcomes may help explain why directionalities of effects sometimes differ, with depressed groups demonstrating higher post-DST cortisol in some studies, but lower post-DST cortisol in others (Lopez-Duran et al. 2009).

Self-Injury, Suicidal Ideation, and HPA Axis Function in Adolescence

In this study, we evaluate associations between HPA axis function—assessed via the DST—and both suicidal ideation

and SII, over-and-above effects of depression and externalizing symptoms. To our knowledge, only three studies have addressed these questions. In a small sample of depressed inpatient and outpatient adolescents, ages 12–18 years, Dahl et al. (1992) reported that DST results were unrelated to suicidal ideation. However, statistical power in that study was limited given the modest number of depressed participants (n=27), only half of whom reported suicidal symptoms. Furthermore, the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS; Kaufman et al. 1997), which was used in the study, is somewhat limited as a measure of suicidal ideation, and does not assess SII. The sample was also 41 % male, which could obscure relations between HPA axis function and clinical outcomes among females. In fact, most DST studies of depressed children and adolescents have enrolled a plurality of males (Lopez-Duran et al. 2009), which is problematic given well characterized sex differences in cortisol responses to stress (Kirschbaum et al. 1992), greater resistance to glucocorticoid feedback among females (Young 1998), and stronger links between cortisol reactivity and internalizing behaviors for girls versus boys (Natsuaki et al. 2009). Furthermore, adolescent females carry almost twice the risk of depression, and attempt suicide at three times the rate of males (Merikangas et al. 2010; Nock et al. 2013). Thus, generalizability to girls of findings from research conducted with mixed sex samples may be limited.

In a second study of somewhat younger inpatient children, ages 6–12 years, Pfeffer et al. (1991) reported that although baseline cortisol was associated with suicidal behavior, post-DST cortisol was not. In this study, over 70 % of participants were male, and almost 60 % were diagnosed with conduct disorder. The relevance of these findings for adolescent females is therefore also unknown.

Finally, Kaess et al. (2012) evaluated the association between HPA axis dysfunction and SII among 14 self-injuring adolescent females, compared with controls. Attenuated salivary cortisol reactivity following a social stress task was observed in the SII group. Although the sample was small, exclusion of males was a strength given sex differences in HPA axis function noted above. This preliminary finding is important because it suggests suppressed HPA axis responding among self-injuring adolescent girls, consistent with our previous discussion of possible mechanisms (see above). As also noted above, however, salivary cortisol assesses a different aspect of HPA axis function (reactivity) than the DST (integrity of negative feedback). Kaess et al. note this in suggesting directions for future research.

Joiner's Acquired Capacity Model

Although articulated primarily at the behavioral level of analysis, Joiner's (2005) acquired capacity hypothesis also points toward blunted stress responding in the pathophysiology of self-injury and suicide. According to this perspective, repeated exposure to painful and/or fearful experiences leads to down-regulation of self-preservation instincts (see Joiner et al. 2009), and desensitization of the normal human stress response. Past suicidal behaviors result in habituation to pain and fear, which would ordinarily evoke a strong stress response. Over time, accruing habituation leads to further down regulation of stress responding and increased likelihood of more severe self-harm and potential for suicide. This theory predicts less cortisol reactivity to dexamethasone challenge.

To summarize, further research on associations between HPA axis function, suicidal ideation, and SII among adolescent females is needed given (1) high rates of suicidal ideation and SII among depressed adolescent females (see Crowell et al. 2012; Nock 2010), (2) possible associations between SII—the most reliable behavioral predictor of eventual suicide—and aberrant cortisol responding (Hamza et al. 2012; Kaess et al. 2012), (3) evidence that the DST marks vulnerability to self-injury and suicide more specifically than it marks vulnerability to depression (Coryell and Schlesser 2008; Roy et al. 1986), and (4) recent theories that implicate down regulation of the stress response system in the pathophysiology of self-injury and suicide.

Following from this discussion, our primary objective in conducting this study was to evaluate—among adolescent girls with histories of depression or depression and self-injury—post-DST cortisol as a correlate of both current suicidal ideation, and retrospective reports of SII, *over-and-above effects of internalizing and externalizing psychopathology*. Thus, we sought to determine whether the DST is associated with suicidal ideation and SII *after* any prediction afforded by depression and conduct problems. Any association between post-DST cortisol and these important clinical outcomes would suggest a need for additional, prospective research. Despite inconsistencies in directionalities of findings across studies and age groups (see above; Lopez-Duran et al. 2009), and different patterns of HPA axis reactivity for females versus males (Kirschbaum et al. 1992), we predicted a negative correspondence between post-dexamethasone cortisol and both SII and suicidal ideation, following from recent theoretical models (e.g., Joiner 2005; Klengel et al. 2013).

Method

Participants and Procedure

Data were collected as part of a broader study of adolescent major depression and SII, described in detail elsewhere (e.g., Crowell et al. 2012, 2013). Participants included 57 adolescent females, ages 13–17 years, with histories of either major depression (n=28), or depression and self-harm (n=29).

Study procedures were approved by the institutional review board at Seattle Children's Hospital. Participants were recruited using classified ads, banners displayed on busses, brochures distributed at local schools, inpatient treatment facilities, outpatient clinics, and ads distributed through direct mailings. Self-injuring and depressed participants were recruited in roughly equal numbers from community (depressed=56 %; SII=46 %) and clinical settings (depressed=44 %; SII=54 %), $\chi^2(1)=0.30$, $p=.59$.

Phone Screen Interested participants and their mothers contacted study personnel initially by phone, and were interviewed separately to assess preliminary inclusion and exclusion criteria, using a screening interview that was administered by a trained research assistant. The interview included (1) mother-report questions about adolescent symptoms of depression from the Adolescent Symptom Inventory (ASI; Gadow and Sprafkin 1997), (2) self-report questions about adolescent symptoms of depression using the Youth's Inventory (YI; Gadow et al. 2002), and (3) both mother- and self-report symptoms of self-injury using the Lifetime Self-Injury Count (L-SASI; Linehan et al. 2006). Adolescent/mother dyads were invited for a subsequent lab visit, described below, if they endorsed items consistent with at least one adolescent episode of unipolar depression in the past year, defined as five or more symptoms above threshold (≥2 on a 0–3 scale; see Gadow and Sprafkin 1997; Gadow et al. 2002) based on self-report, and 4 or more symptoms above threshold based on parent report. To be included in the self-injury group, potential adolescent participants also had to report having engaged in 3 or more episodes of self-injury in the past 6 months, or 5 or more lifetime. At least 1 of these episodes must have occurred in the prior 6 months. Histories of self-injury and diagnoses of depression were confirmed/disconfirmed at a subsequent lab visit using the full L-SASI (Linehan et al. 2006) and the K-SADS (Kaufman et al. 1997), respectively (see below).

Potentially depressed participants were excluded if they reported any lifetime SII. Symptoms consistent with mania, mental retardation, and schizophrenia spectrum diagnoses were exclusions for both groups. Participants were also excluded if they were currently taking beta blockers, mood stabilizers, benzodiazepines, or recreational drugs (confirmed via urinalysis) the week of DST assessment. Adolescents who were taking oral contraceptives were also excluded due to potential effects on the DST. A 36-h washout was required for those who were taking stimulants.

Lab Visit After informed consent and assent were obtained, adolescents and their mothers were escorted into separate rooms where they each completed several measures, described in detail below. Adolescents provided self-reports of psychopathology, behavior problems, and substance use. Mothers provided reports of their daughter's psychopathology and behavior problems using the Child Behavior Checklist (Achenbach 1991a). During this visit, adolescents and their mothers were also interviewed separately by a trained graduate research assistant, who obtained more detailed reports of psychopathology and SII. Past year major depression diagnoses were assessed by the second author using the K-SADS, which has excellent psychometric properties (Kaufman et al. 1997). All but one participant met criteria on both the adolescent- and mother-reported K-SADS interview. That participant was excluded. For purposes of this study, K-SADS data were not used. Rather, we analyzed depression severity using continuous scores obtained from the ASI and the YI. This was important given our analytic approach (see below).

Adolescents and their mothers also reported on the adolescent's self-injury using the full L-SASI (Linehan et al. 2006). Regardless of group status based on the phone interview (see above), all parents and adolescents were asked to report on whether the adolescent had ever self-injured. Affirmative responses were followed with administration of the full L-SASI. The L-SASI is a structured interview for gathering information regarding suicidal intent, lethality, method, and level of medical treatment received for the first, most recent, and most severe episodes of self-injury. With interviewer assistance, participants tally the number of lifetime self-injury events, by method, with different tallies for self-injury with suicidal intent, without intent, and with ambivalent intent. Within each method, participants also describe the highest lethality and medical intervention received. Lethality rankings range from 1=*very low* (e.g., scratching, "overdose" by 2–4 pills), to 6=*severe* (e.g., jumping from high places, Russian roulette, asphyxiation). Medical interventions are tallied to reflect the number of visits to a physician/nurse, ER, or ICU. There are no psychometric studies of the L-SASI. However, items are identical to a longer measure, the Suicide Attempt Self-Injury Interview, which has very good inter-rater reliability and adequate validity (Linehan et al. 2006).

Adolescent self-report measures included the full YI (Gadow et al. 2002), the Youth Self-Report (YSR; Achenbach 1991b), the Suicidal Ideation Questionnaire (SIQ; Reynolds and Mazza 1999), and a comprehensive questionnaire assessing onset, frequency, and problems associated with substance use (Hawkins and Catalano 2001). The 120-item YI is a self-report checklist that yields dimensional scores and diagnostic cutoffs for several *DSM-IV* (American Psychiatric Association 2000) Axis I disorders. Items are rated on 4-point scales (0=*never* to 3=*very often*), with a score of 2 or higher considered positive for each symptom. In this paper, we analyze both the number of symptoms scored 2 or higher for depression, and dichotomous diagnoses (see below). Sensitivity and specificity of the YI scales are adequate to excellent (Gadow et al. 2002). The YSR is a 112-item measure

of adolescent behavior problems, including several psychopathology subscales and broadband internalizing and externalizing factors, which are used in the current study. As with the parent-report CBCL, YSR symptoms are assessed on 3-point scales (0=*never* to 2=*often*), which are summed and converted to *T*-scores (*M*=50, *SD*=10). The YSR is widely used and has excellent psychometric properties (Achenbach 1991b). The substance use questionnaire assesses whether or not adolescents have tried a number of substances, including alcohol, age at first use, and the number of times used in the past month. At the end of the questionnaire there are several yes/no questions regarding problems associated with use (e.g., has substance use ever caused problems with family or friends). A total problem score is created by summing questions regarding problematic use (range=0-15).

Finally, adolescents and their mothers completed a review of systems with a physician, who screened for any medical condition that might interfere with the validity of the DST (e.g., Cushing syndrome) or any potential adverse effects (e.g. drug interactions). Adolescents were also required to take a urine pregnancy test, which was administered by a registered nurse. No participants were excluded based on the review of systems or pregnancy test. At the end of the visit, adolescents and their mothers were given a 1 mg dose of oral dexamethasone and instructed to administer the medication at precisely 11 pm the night before the second visit, when the DST assessment occurred. Participants were paid $30 for the Lab Visit.

Blood Draw On the day before the blood draw, research staff called participants to remind them about the 11 pm administration of dexamethasone. All participants reported taking the dose at 11 pm±5 min. All appointments were scheduled for 3:30 pm, which allowed 30 min for consent/assent prior to the 4 pm blood draw. At 3:50 pm, adolescents were taken to a comfortable exam room with an armchair, and offered EMLA numbing cream if they chose. A registered nurse initiated the blood draw at 3:57, and all procedures were completed by 4:10 pm. Participants who arrived to the second visit late, or forgot to take the dexamethasone pill were rescheduled. Blood samples were processed at the Seattle Children's Hospital laboratory. Participants were paid another $30 for the blood draw.

Results

Demographics and descriptive statistics appear in Table 1. No differences between depressed and self-injuring participants were found on any demographic variable, or on post-DST cortisol levels. Using a traditional≥5 μg/dl threshold, only one adolescent was classified as a DST non-suppressor. Cortisol data were missing for 4 participants in the depressed only group and 2 participants in the self-injury group (10.5 % of the sample). These participants were either unable to tolerate the blood draw, or the nurse could not locate a suitable vein. Missing data on the parent and self-report measures ranged from n=0 to n=3 (0–5.3 %). All missing values were imputed following current recommendations (see Graham 2009) by creating 10 data sets in SPSS 20. Multiple imputation is more accurate than both listwise deletion and mean substitution of missing data, and reduces selection biases in dependent measures (see Acock 2005).

For parent- and self-report measures of internalizing and externalizing psychopathology, only one group difference emerged—on YSR externalizing behavior—where the self-injury group scored higher than depressed only participants, $F(1,55)=14.5$, $p<0.001$. The self-injury group also scored higher on substance use than the depressed-only group, $F(1,55)=22.7$, $p<0.001$. As expected given our recruitment strategy, self-injuring participants scored higher on both the SIQ, $F(1,55)=23.7$, $p<0.001$, and the LSASI, $F(1,55)=28.8$, $p<0.001$. Further details about the sample are reported elsewhere (Crowell et al. 2012, 2013). For purposes of this study, all participants were pooled into a single group for further analysis given no differences in levels of depression, internalizing psychopathology, or post-DST cortisol levels.

Sample-wide correlations among study variables appear in Table 2. Significant negative associations were observed between post-DST cortisol levels and SIQ scores, self-reported depression symptoms, self-reported depression diagnoses, and self-reported externalizing behaviors, all rs≤−0.28, all ps≤0.05. These negative bivariate correlations are consistent with a stronger negative feedback loop in the HPA axis among those who scored highest on suicidal ideation and depression. As might be expected, SIQ and L-SASI scores were also correlated significantly, $r=0.37$, $p<0.01$. Readers are referred to Table 2 for additional correlations.

Post-DST Cortisol as an Independent Predictor of Current Suicidal Ideation

Combined Parent-/Self-Report Composites Evaluation of post-DST cortisol as a predictor of current suicidal ideation, over-and-above (1) combined parent-/self-reports, (2) parent-reports, and (3) self-reports of internalizing and externalizing psychopathology was accomplished with a series of simultaneous multiple linear regressions (MLRs). For each informant (combined, parent, self), main effects of internalizing behavior, externalizing behavior, and post-DST cortisol levels were entered as predictors of SIQ total scores. In the first set of MLRs, we evaluated combined parent-/self-reports in three models, including (1) a CBCL (parent)/YSR (adolescent) dimensional composite model (Model 1), (2) an ASI

Table 1 Demographic characteristics and descriptive statistics by group

Variable	Group		Test-statistic	Effect size (partial η^2)
	Depressed (n=28)	Self-injuring (n=29)		
Adolescent's age (years)	15.7 (1.4)	16.3 (1.0)	F=3.8	0.07
Number (and %) minority	8 (24 %)	5 (15 %)	χ^2=0.8	0.01
Family income (thousands)	58.6 (32.9)	68.5 (31.2)	F=1.3	0.02
Post-DST cortisol level (μg/dl)	1.9 (2.6)	1.2 (0.8)	F=2.4	0.05
Substance use composite	1.3 (2.1)	7.6 (6.7)	F=22.7***	0.29
Suicidal Ideation Questionnaire total[a]	22.2 (22.7)	60.7 (39.5)	F=23.7***	0.33
Lifetime Suicide Attempt Self-Injury count[a]	0.0 (0.0)	143.5 (288.7)	F=28.8***	0.36
K-SADS past year depression diagnosis (%)	28 (100 %)	29 (100 %)	χ^2=0.0	0.89
ASI current depression symptoms	3.3 (2.5)	3.5 (2.5)	F=0.1	<0.01
ASI current depression diagnosis (%)	6 (21 %)	10 (34 %)	χ^2=1.2	0.02
YI current depression symptoms	5.6 (3.5)	6.7 (3.0)	F=1.8	0.03
YI current depression diagnosis (%)	14 (50 %)	21 (72 %)	χ^2=3.0	0.05
CBCL internalizing T-score	69.1 (7.8)	65.4 (9.2)	F=2.2	0.05
YSR internalizing T-score	60.2 (10.2)	65.9 (11.8)	F=3.6	0.06
ASI current conduct disorder symptoms	0.3 (0.7)	0.6 (1.3)	F=1.4	0.03
ASI current conduct disorder diagnosis (%)	0 (0 %)	3 (10 %)	χ^2=3.2	0.06
YI current conduct disorder symptoms	0.5 (0.7)	0.8 (0.7)	F=2.4	0.04
YI current conduct disorder diagnosis (%)	2 (7 %)	3 (10 %)	χ^2=0.7	<0.01
CBCL externalizing T-score	56.1 (10.3)	60.9 (10.1)	F=2.6	0.04
YSR externalizing T-score	55.5 (9.7)	65.0 (8.6)	F=14.5***	0.22

Continuous variables are expressed as mean (*SD*)

DST dexamethasone suppression test, *ASI* Adolescent Symptom Inventory, *CBCL* Child Behavior Checklist, *K-SADS* Kiddie Schedule for Affective Disorders and Schizophrenia, *YI* Youth Inventory, *YSR* Youth Self Report

***p<0.001

[a] Descriptive statistics are reported on raw scores, but F-statistics are computed on square root-transformed scores

(parent)/YI (adolescent) dimensional composite model (Model 2), and (3) an ASI (parent)/YI (adolescent) diagnostic composite model (Model 3). For the CBCL/YSR dimensional model, an internalizing composite was computed by calculating z-scores for parent-reports (CBCL) and self-reports (YSR) and adding them to form a single CBCL/YSR predictor. The same process was used to form a CBCL/YSR externalizing composite. These composites, which reduced the number of predictors by half, were entered in a simultaneous MLR along with post-DST cortisol levels, predicting SIQ total scores. In simultaneous MLR, the significance of each predictor (i.e., internalizing, externalizing, cortisol) variable reflects its independent association with the dependent variable (i.e., suicidal ideation), over-and-above all other predictors in the equation (i.e., as if it were entered into the regression equation last). Thus, there is no need to conduct hierarchical regressions to obtain increments in prediction afforded by single predictors (see e.g., Pedhazur 1997). Results appear at the top portion of Table 3 (Model 1). Both the CBCL/YSR internalizing composite, $t(53)=2.90$, $p=0.007$, and post-DST cortisol levels, $t(53)=-2.02$, $p=0.052$, predicted SIQ scores, over-and-above all other variables in the model. The CBCL/YSR externalizing composite did not, $t(53)=1.68$, $p=0.103$. This model accounted for a large portion (45.1 %) of the variance in current suicidal ideation.

Results from the MLR using ASI/YI symptom composites (Model 2) appear next in Table 3. Both ASI/YI major depression symptoms $t(53)=4.21$, $ps<0.001$, and post-DST cortisol levels, $t(53)=-2.19$, $p=0.034$, predicted suicidal ideation, over-and-above other variables in the model. The ASI/YI conduct disorder symptom composite did not, $t(53)=-0.39$, $p=0.969$. However, the ASI/YI model accounted for far less of the variance (26.8 %) in suicidal ideation than the CBCL/YSR model (45.1 %).

In the final MLR of combined parent-/self-reports, ASI/YI diagnostic composites were formed for both depression and CD using an "or" algorithm. Participants were assigned a 1 for depression if they met current *DSM-IV* diagnostic criteria based on either parent- (ASI) or self- (YI) report. All others were assigned a 0. Similarly, participants were assigned a 1 for

Table 2 Variable correlations

Variable	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
1. Post-DST cortisol level	−0.28*	−0.09	−0.13	−0.23	−0.16	−0.28*	−0.35**	−0.44**	−0.15	−0.13	−0.07	0.20	0.14	−0.17	0.19
2. Suicidal Ideation Questionnaire total score	–	0.37**	0.29*	0.22	0.15	0.16	0.28*	0.49***	0.55***	0.24	0.15	0.16	0.28*	0.34**	0.14
3. Lifetime Suicide Attempt Self-Injury count		–	0.41**	0.19	0.08	−0.03	0.04	0.32*	0.05	0.24	0.28*	−0.02	0.07	0.05	0.34*
4. Self-report substance use			–	0.26*	−0.15	0.18	0.14	0.50***	0.27*	0.26*	0.35**	0.05	0.00	0.36**	−0.18
5. Self-report CD symptoms (YI)				–	0.77***	0.34**	0.36**	0.53***	0.33**	0.36**	0.30*	0.28*	0.25	0.13	−0.15
6. Self-report CD diagnosis (YI)					–	0.23	0.25	0.30*	0.15	0.22	0.20	0.18	0.22	0.04	−0.12
7. Self-report MDE symptoms (YI)						–	0.76***	0.52***	0.58***	0.09	−0.11	0.13	0.20	0.24	0.17
8. Self-report MDD diagnosis (YI)							–	0.54***	0.52***	0.26*	0.02	0.08	0.17	0.24	0.06
9. YSR externalizing score								–	0.64***	0.17	0.05	0.09	0.22	0.46***	−0.09
10. YSR internalizing score									–	0.00	−0.02	0.15	0.32*	0.22	0.23
11. Parent-report CD symptoms (ASI)										–	0.75***	0.28*	0.09	0.37**	−0.02
12. Parent-report CD diagnosis (ASI)											–	0.19	0.03	0.22	−0.18
13. Parent-report MDE symptoms (ASI)												–	0.80***	0.18	0.60***
14. Parent-report MDD diagnosis (ASI)													–	0.14	0.51***
15. CBCL externalizing score														–	0.33*
16. CBCL internalizing score															–

Both SIQ and LSASI scores were square root transformed to achieve univariate normality

CD conduct disorder, *DST* dexamethasone suppression test, *MDD* major depressive disorder, *MDE* major depressive episode, *ASI* Adolescent Symptom Inventory, *CBCL* Child Behavior Checklist, *YI* Youth Inventory, *YSR* Youth Self Report

*$p \leq 0.05$. **$p \leq 0.01$. ***$p \leq 0.001$

Table 3 Multiple regressions with current suicidal ideation (SIQ total) as the dependent variable

Model	Measure	Predictor	*b*	*t*	*p*	partial *r*	model R^2
	Combined parent/child report						
1	CBCL/YSR scale composite	Externalizing score	0.53	1.68	0.103	0.081	**0.451**
		Internalizing score	**1.03**	**2.90**	**0.007**	**0.403**	
		Post dexamethasone cortisol	**−0.43**	**−2.02**	**0.052**	**−0.182**	
2	ASI/YI symptom composite	Conduct disorder symptoms	−0.01	−0.39	0.969	0.039	**0.268**
		Major depression symptoms	**1.33**	**4.21**	**<0.001**	**0.484**	
		Post dexamethasone cortisol	**−0.45**	**−2.19**	**0.034**	**−0.163**	
3	ASI/YI diagnosis (or algorithm)	Conduct disorder diagnosis	−0.62	−0.49	0.643	0.061	**0.207**
		Major depression diagnosis	**2.58**	**2.72**	**0.009**	**0.392**	
		Post dexamethasone cortisol	**−0.49**	**−2.13**	**0.038**	**−0.177**	
	Parent-reports						
4	CBCL	Externalizing score	0.08	1.74	0.090	0.142	**0.217**
		Internalizing score	0.06	1.25	0.222	0.205	
		Post dexamethasone cortisol	**−0.53**	**−2.36**	**0.024**	**−0.214**	
5	ASI	Conduct disorder symptoms	0.38	0.85	0.399	0.142	0.089
		Major depression symptoms	0.23	1.29	0.205	0.185	
		Post dexamethasone cortisol	**−0.53**	**−2.14**	**0.038**	**−0.212**	
6	ASI diagnosis (current)	Conduct disorder diagnosis	1.57	0.76	0.449	0.137	**0.130**
		Major depression diagnosis	**2.00**	**2.24**	**0.030**	**0.256**	
		Post dexamethasone cortisol	**−0.55**	**−2.37**	**0.022**	**−0.209**	
	Self-reports						
7	YSR	Externalizing score	0.01	0.01	0.989	−0.041	**0.389**
		Internalizing score	**2.18**	**3.79**	**<0.001**	**0.416**	
		Post dexamethasone cortisol	−0.36	−1.64	0.108	−0.195	
8	YI	Conduct disorder symptoms	0.07	0.60	0.549	0.095	**0.222**
		Major depression symptoms	**0.32**	**4.45**	**<0.001**	**0.519**	
		Post dexamethasone cortisol	−0.20	−0.95	0.349	−0.020	
9	YI diagnosis (current)	Conduct disorder diagnosis	−0.10	−0.07	0.942	0.027	**0.203**
		Major depression diagnosis	**2.47**	**2.64**	**0.011**	**0.431**	
		Post dexamethasone cortisol	−0.26	−1.08	0.287	−0.070	

All Significant effects are **bolded**

ASI Adolescent Symptom Inventory, *CBCL* Child Behavior Checklist, *SIQ* Suicidal Ideation Questionnaire, *YI* Youth Inventory, *YSR* Youth Self Report

CD if they met current *DSM-IV* diagnostic criteria based on either parent- (ASI) or self- (YI) report. All others were assigned a 0.

Results from these analyses appear next in Table 3 (Model 3). Consistent with results from the dimensional model (Model 2), both ASI/YI major depression diagnosis $t(53)=2.58$, $p=0.009$, and post-DST cortisol levels, $t(53)=-2.13$, $p=0.038$, predicted suicidal ideation, over-and-above other variables in the model. The ASI/YI conduct disorder diagnosis composite did not, $t(53)=-0.62$, $p=0.643$. This model accounted for 20.7 % of the variance in suicidal ideation. Thus, in all three parent-/self-report composite models, internalizing symptoms and post-DST cortisol levels provided independent prediction of current suicidal ideation.

Parent-Only Reports To evaluate parent-reports as predictors of SIQ scores, we ran parallel MLRs, substituting (1) CBCL scores (internalizing, externalizing), (2) ASI dimensional scale scores (depression symptoms, CD symptoms), and (3) ASI diagnoses (MDD, CD) for the composites described immediately above. Results are reported in the middle third of Table 3 (Models 4–6). Post-DST cortisol levels emerged as an independent predictor of adolescent's SIQ scores in each model, all ts$(53)\leq-2.14$, all ps≤0.038. In addition, MDD diagnoses predicted suicidal ideation in the categorical model, $t(53)=2.24$, $p=0.030$. All other measures of internalizing symptoms, externalizing symptoms, depression, and CD were non-significant, all ts$(53)\leq1.74$, all ps≥0.090. These models accounted for far less variance in suicidal ideation (13.0–

21.7 %) than the parent-report/self-report composite models described above.

Self-Reports Analyses of self-reports as predictors of suicidal ideation appear in the bottom third of Table 3 (Models 7–9). These models included YSR scores (internalizing, externalizing), YI dimensional scale scores (depression symptoms, CD symptoms), YI diagnoses (MDD, CD), and post-DST cortisol as predictors of SIQ scores. Internalizing symptoms (Model 7), depression scores (Model 8), and depression diagnoses (Model 9) were significant across the MLRs, all ts(53)≥ 2.64, all ps≤0.011. Externalizing behaviors (Model 7), CD symptoms/diagnoses (Model 8), and post-DST cortisol levels (Model 9) were not, all ts(53)≤1.64, all ps≥0.108. In general, these self-report models accounted for more variance in suicidal ideation (20.3–38.9 %) than parent-reports, but less variance than parent-/self- composite reports.

Post-DST Cortisol as an Independent Predictor of Retrospectively Reported Self-Injury

Evaluation of post-DST cortisol, combined reports, parent-reports, and self-reports of internalizing and externalizing psychopathology as predictors of lifetime self-injury events, assessed by the LSASI, was accomplished with similar approach to that described above. However, rather than using MLR, we used negative binomial regression (see Hilbe 2011) to accommodate the zero-inflated SII data in which all members of the depressed only group reported no self-harm events (SII was an exclusion criterion for depressed only participants; see above). These regressions (Models 10–18) appear in Table 4. The far right column, labeled exp(b), indicates effect size for each parameter (analogous to an odds ratio in logistic regression). The general pattern of results was similar to that found for suicidal ideation. Post dexamethasone cortisol accounted for significant variance in past SII in 5 of the 6 combined informant and parent-report models, all χ^2s(1)≥ 3.68, all ps≤0.055. In contrast, cortisol was not an independent predictor of SII in any of the self-report models.

Discussion

Our primary objective was to evaluate associations between post-DST cortisol and both current suicidal ideation and retrospective reports of SII among adolescent girls with histories of major depression or depression and self-harm. In 11 of the 12 combined and parent-report models, post-DST cortisol was associated independently with current suicidal ideation and past SII among adolescents, over-and-above variance accounted for by internalizing and externalizing symptoms. The CBCL/YSR model accounted for almost half (45.1 %) of the variance in suicidal ideation—an extremely important clinical outcome. Although a previous study of adolescents indicated no relation between suicidality and post-DST cortisol (Dahl et al. 1992), that study was smaller, included males and females, and used a less comprehensive measure of suicidal ideation. Interestingly, although post-DST cortisol was associated with suicidal ideation and SII in the parent-report models, it was not in the self-report models, where only internalizing symptoms were associated with current suicidal ideation, and both internalizing and externalizing symptoms were associated with past SII. Importantly, however, the self-report models accounted for far less variance than the combined parent-/self-report models. Thus, consistent with other findings in the literature, parent-reports and self-reports provided unique yet augmentative information about adolescent psychopathology (De Los Reyes and Kazdin 2005).

In all models in which post-DST cortisol was significant, it was correlated negatively with suicidal ideation and SII. Thus, lower post-DST cortisol was associated with greater suicidal ideation, and higher retrospective reports of SII. Lower post-dexamethasone cortisol suggests an efficient negative feedback loop in which administration of dexamethasone suppressed cortisol production. Although the causal mechanism for this association is not clear, it appears to be consistent with findings of attenuated salivary cortisol responding to social stress among adolescent girls who engage in SII (Kaess et al. 2012). In the present study, less cortisol reactivity to dexamethasone was observed, whereas in the latter, less cortisol reactivity to interpersonal stress was found. Importantly, our findings cannot be explained by group status, since post-DST cortisol levels were unrelated to group membership.

These findings are consistent with Joiner's (2005) interpersonal–psychological theory, which suggests that that self-harm and suicide develop in part from acquired capacity to engage in ever more painful and fearful behaviors through habituation mechanisms, which down regulate normal stress responding over time. Although Joiner's theory does not provide a neurobiological mechanism, one possibility is that glucocorticoid responding becomes altered through epigenetic mechanisms. A growing body of potentially related research indicates that hypocortisolaemia is common among depressed children who experienced abuse, maltreatment, and/or other forms of trauma early in life (e.g., Cullen et al. 2013; Gunnar and Vazquez 2001; Wikgren et al. 2012), and is likely conferred epigenetically (see Doom and Gunnar 2013; McGowan et al. 2009). Recently, Klengel et al. (2013) proposed that excess cortisol reactivity to severe early life stress induces DNA methylation in glucocorticoid response elements at the *FKBP5* gene locus. In turn, these epigenetic alterations in DNA structure produce enduring changes in glucocorticoid feedback, and increase risk for stress-related psychiatric morbidity—particularly PTSD and depression. This model provides a mechanism through which effects of allostatic load on

Table 4 Negative binomial regressions with retrospective reports of self-injury (L-SASI total) as the dependent variable

Model	Measure	Predictor	*b*	χ^2	*p*	effect size exp(*b*)
	Combined parent/child report					
10	CBCL/YSR scale composite	**Externalizing score**	**0.36**	**30.88**	**<0.001**	**1.44**
		Internalizing score	**0.45**	**15.00**	**<0.001**	**1.57**
		Post dexamethasone cortisol	**−0.33**	**8.03**	**0.005**	**0.72**
11	ASI/YI symptom composite	Conduct disorder symptoms	0.15	1.99	0.159	1.16
		Major depression symptoms	**0.84**	**29.58**	**<0.001**	**2.31**
		Post dexamethasone cortisol	**−0.20**	**3.68**	**0.055**	**0.82**
12	ASI/YI diagnosis (or algorithm)	Conduct disorder	0.40	0.92	0.339	1.49
		Major depression	**1.13**	**22.00**	**<0.001**	**3.09**
		Post dexamethasone cortisol	**−0.33**	**9.33**	**0.002**	**0.72**
	Parent-reports					
13	CBCL	**Externalizing score**	**0.07**	**35.59**	**<0.001**	**1.07**
		Internalizing score	**0.04**	**5.32**	**0.021**	**1.04**
		Post dexamethasone cortisol	**−0.42**	**10.10**	**0.001**	**0.66**
14	ASI	**Conduct disorder symptoms**	**0.33**	**6.17**	**0.013**	**1.39**
		Major depression symptoms	−0.41	0.59	0.237	0.95
		Post dexamethasone cortisol	−0.18	1.90	0.152	0.85
15	ASI diagnosis (current)	**Conduct disorder diagnosis**	**1.42**	**4.75**	**0.029**	**4.16**
		Major depression diagnosis	0.29	0.65	0.419	1.34
		Post dexamethasone cortisol	**−0.28**	**5.92**	**0.020**	**0.75**
	Self-reports					
16	YSR	**Externalizing score**	**0.06**	**26.91**	**<0.001**	**1.07**
		Internalizing score	0.01	0.62	0.431	1.01
		Post dexamethasone cortisol	−0.06	0.26	0.611	0.94
17	YI	**Conduct disorder symptoms**	**0.72**	**17.28**	**<0.001**	**2.06**
		Major depression symptoms	**0.19**	**9.41**	**0.002**	**1.22**
		Post dexamethasone cortisol	0.21	3.10	0.078	1.27
18	YI diagnosis (current)	Conduct disorder diagnosis	0.62	1.60	0.205	1.85
		Major depression diagnosis	**0.87**	**12.25**	**<0.001**	**2.38**
		Post dexamethasone cortisol	−0.12	1.13	0.287	0.89

Significant effects are **bolded**

ASI Adolescent Symptom Inventory, *CBCL* Child Behavior Checklist, *SIQ* Suicidal Ideation Questionnaire, *YI* Youth Inventory, *YSR* Youth Self Report

the HPA axis may operate. According to the allostatic load framework, excessive activation of the HPA axis and other neural/hormonal systems early in life leads to long-term down-regulation in their functional operating ranges (in this case through more efficient negative feedback), oftentimes with adverse consequences for health and wellbeing (see Klengel et al. 2013; Lupien et al. 2009). Exposure to maltreatment, abuse, and other forms of adversity may initiate a cascade of epigenetic and neural responses among vulnerable individuals, resulting in anhedonia avolition, and social isolation (see Beauchaine et al. 2011). Individuals who possess vulnerability genes and incur trauma may be especially likely to engage in self-harm. As noted above, we did not assess maltreatment or child abuse in this sample, so we discuss this potential mechanism with caution. However, among self-injuring samples, and among those with BPD, rates of child maltreatment and child abuse are quite high (e.g., Maniglio 2011; Norden et al. 1995; see also Beauchaine et al. 2009; Yates 2009).

A second, perhaps related mechanism through which HPA-axis function might be linked to both self-harm and suicidal ideation involves the locus coeruleus-norepinephrine (LC-NE) system. As we have reviewed elsewhere (Beauchaine et al. 2011), this system is comprised of noradrenergic projections that originate in the locus coeruleus, and project throughout the hippocampus, hypothalamus, spinal cord, cerebellum, frontal cortex, and somatosensory cortices (see Simpson and Lin 2007). Tonic NE function is associated with non-specific arousal, vigilance, and attention, whereas phasic activation of the LC-NE system through exposure to attention-evoking

stimuli and stressors facilitates classical conditioning and promotes active avoidance (escape) behaviors (e.g., Aston-Jones et al. 2007; Detke et al. 1995). Importantly, both self-harm and suicide often serve escape functions (see e.g., Linehan 1993; Crowell et al. 2009). Thus, LC-NE activation subserves coping efforts in the face of stress (Cecchi et al. 2002). This occurs primarily through modulating effects of NE on other neural systems, including the HPA axis (see Morilak 2007).

In addition to their aforementioned implications for self-injury and suicidal ideation, compromises in developing LC-NE and HPA axis systems, and associated difficulties with social affiliation, may help explain (1) why so many adolescents who are recruited based solely on self-injury already meet criteria for BPD, and (2) why adolescent self-injury marks significant risk for development of BPD. It is well known that many adolescents who engage in self-injury incurred maltreatment and/or abuse as children, as have many adults with BPD (Maniglio 2011; Norden et al. 1995; see also Beauchaine et al. 2009; Yates 2009). Growing evidence points toward enduring, epigenetically-mediated alterations in HPA axis and LC-NE system function, with associated impairments in social affiliation and sensitivity to others. These are core components of personality disturbance observed in BPD.

Our findings are inconsistent with reports in the adult literature which link DST *non-suppression* to suicide, especially at long-term follow up of inpatient samples (Coryell and Schlesser 1981, 2008; Roy et al. 1986). Our findings are also inconsistent with two null findings from inpatient and mixed inpatient/outpatient samples of children/adolescents (Dahl et al. 1992; Pfeffer et al. 1991). However, in contrast to these studies, only one participant in our sample was classified as a DST non-suppressor, and all of our participants were female. More often than not, the DST is used among inpatient samples (see above), where depression is more acute and more severe. Nevertheless, participants in our study were considerably distressed, and comprise a high-risk demographic in which rates of SII, suicide attempts, and completed suicide are both increasing and alarmingly high (Crowell et al. 2012; Nock 2010).

Limitations to our study are several. We did not assess pubertal status, which mediates links between cortisol reactivity—albeit to interpersonal stressors—and internalizing behavior among girls (Natsuaki et al. 2009). However, 80 % of adolescents in our study were age 15 years or older, well beyond the average age of menarche. Furthermore, including age (which is correlated with pubertal status) as a covariate in our models changed none of the results (we therefore omitted age for the sake of parsimony), and age is not a significant source of variability in DST outcomes (Dahl et al. 1992; Lopez-Duran et al. 2009).

In addition, we did not measure pre-DST cortisol, which correlates positively with post-DST cortisol (Dahl et al. 1992). Thus, it is impossible for us to know whether low values represent dexamethasone suppression, or a combination of dexamethasone suppression and baseline individual differences in cortisol. Dexamethasone suppression implicates HPA-axis *reactivity* in expression of suicidal ideation and SII, whereas baseline differences in cortisol implicate HPA-axis *activity*. In light of this ambiguity, we have been careful to refer to post-DST cortisol levels rather than DST suppression. However, from a pragmatic standpoint this may matter little given significant prediction of such important clinical outcomes. Nevertheless, authors of future studies may wish to obtain pre- and post-dexamethasone cortisol levels. Notably, however, doing so places a large burden on participants, who must undergo blood draws on consecutive days.

Our sample size, although larger than those in other published reports, was also modest, especially for the number of regressions run. In an effort to ensure that our results were not spurious, we replicated them across informants (parent, self, and combined), measures (syndromal dimensional, *DSM* dimensional, *DSM* categorical), and behavioral constructs (self-injury, suicidal ideation). Nevertheless, future studies with larger samples are needed.

Finally, as pointed out by an anonymous reviewer, blood cortisol is more sensitive to external stressors and increases faster than salivary cortisol, and some individuals have aversive reactions to anticipated blood draws. If any such reactions were systematic (e.g., self-injuring adolescents were less fearful, resulting in lower blood cortisol), our primary dependent variable could be biased. Although we cannot address this directly, we adopted a number of procedures to minimize stress, including (1) drawing blood in the first part of the visit to minimize distress, (2) use of EMLA (numbing) cream, (3) allowing mothers in the room and allowing participants to watch television, (4) ensuring that nurses were well-trained and able to obtain blood quickly, and (5) abandoning blood draws if there were difficulties (see above). Nevertheless, since we did not collect data on participants' reactions to the blood draw, we cannot eliminate the possibility of bias. In future research, adolescents' subjective reactions to blood draws should be assessed.

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