Autonomic correlates of lifetime suicidal thoughts and behaviors among adolescents with a history of depression

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Abstract

Suicidal thoughts and behaviors (STBs) have been associated with emotion dysregulation and atypical responses to affective and stressful stimuli. To investigate the psychophysiology involved, we measured changes in respiratory sinus arrhythmia (RSA) and cardiac preejection period (PEP) (indexing parasympathetic and sympathetic functioning, respectively) in response to stressful and sadness-eliciting laboratory probes. Our sample included adolescents with a history of depression and STBs (n = 177), adolescents with a history of depression but no history of STBs (n = 47), and healthy controls (n = 175). The outcome of interest was the most severe form of clinician-rated STBs across the subject's lifetime. In partial support of our hypotheses, during the stressful task, adolescents with a history of depression and STBs did not evidence the RSA decrease that was exhibited by controls, and displayed greater PEP shortening compared to ever-depressed adolescents with no lifetime STBs. No group differences were found in either RSA or PEP reactivity to the sadness-eliciting stimulus. As expected, severity of STBs was positively correlated with the extent of PEP shortening during the stressful task. The results suggest that adolescents with a history of depression and STBs experience blunted parasympathetic responses to stress along with compensatory efforts. Our findings contribute to a better understanding of STBs among youths and underscore that future studies should examine physiological risk factors for these psychopathological outcomes.

Keywords: suicidal thoughts and behaviors, autonomic nervous system, respiratory sinus arrhythmia, preejection period, adolescents, depression

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1. Introduction

Suicide is a major public health challenge and the second leading cause of death among adolescents in the U.S. (CDC, 2016). As one approach to prevention, suicidal thoughts and behaviors (STBs) have received much attention because they are predictors of completed suicide (for reviews see, Bridge, Goldstein, & Brent, 2006; Franklin et al., 2017; Spirito & Esposito-Smythers, 2006). While STBs are of concern regardless of age, their impact may be particularly negative during adolescence (CDC, 2017; Cha et al., 2018; Nock et al., 2013). Namely, adolescence is characterized by important physiological, cognitive, emotional, and social developmental changes (e.g., Crone & Dahl, 2012; Smetana, Campione-Barr, & Metzger, 2006), which may be disrupted by STBs. Additionally, longitudinal studies found that histories of STBs during adolescence were associated with negative functional outcomes in adulthood (Copeland, Goldston, & Costello, 2017; Goldman-Mellor et al., 2014; Nault-Brière, Rohde, Seeley, Klein, & Lewinsohn, 2015). Prevention of STBs in this age group therefore is needed in order to facilitate normative developmental processes.

The relation between STBs and depression has been well established during adolescence (for a review see, Thapar, Collishaw, Pine, & Thapar, 2012). For example, close to two thirds of adolescents with lifetime STBs have a history of depression, and depression is the most prevalent mental disorder among youths with STBs (Nock et al., 2013). The prevalence of STBs is higher among adolescents with a history of depression as compared to those with no lifetime depression (Kovacs, Goldston, & Gatsonis, 1993). Additionally, among depressed children and adolescents, histories of STBs are associated with more severe depressive symptoms (Liu et al., 2006).

Given the importance of early identification and prevention of STBs, researchers have sought to identify modifiable mechanisms that may potentially also function as risk factors. Emotion regulation is one such mechanism that has been implicated in STBs (Zlotnick, Donaldson, Spirito, & Pearlstein, 1997). According to the emotion-regulation conceptual framework of STBs, suicidal behaviors are the outcomes of high levels of negative affect (mostly depressed, dysphoric mood), which an individual has not been able to control or downregulate (e.g., Baumeister, 1990; Linehan, 1993; Shneidman, 1998). Thus, STBs become the avenues through which the individual seeks to interrupt or terminate intolerable dysphoria. Indeed, high levels of negative affect have been reported in various samples of suicidal people (e.g., Nock, Wedig, Holmberg, & Hooley, 2008; You, Talbot, He, & Conner, 2012). More to the point, individuals with STBs have been shown to have higher levels of emotion dysregulation than normal controls , based both on self-report questionnaires (e.g., Khazem & Anestis, 2016; Miranda, Tsypes, Gallagher, & Rajappa, 2013; Pisani et al., 2013; Rajappa, Gallagher, & Miranda, 2012; Saffer, Glenn, & Klonsky, 2015) and laboratory performance (e.g., Keilp et al., 2013; Pollock & Williams, 2004; Williams & Broadbent, 1986). Additionally, more severe forms of STBs have been associated with worse emotion regulation. For example, among adolescent psychiatric inpatients, suicide attempters reported higher levels of emotion dysregulation compared to those with suicidal ideation only (Zlotnick et al., 1997). Likewise, among youths with a history of depression and STBs, more severe forms of STBs were associated with more maladaptive ways of regulating dysphoria (Tamás et al., 2007).

However, in prior research on STBs, affective responses and emotion regulation were mostly assessed via self-ratings, which rely on subjective judgment and may be influenced by social desirability and recall bias (Hunt, Auriemma, & Cashaw, 2003). In contrast, a more

objective metric of the experience and regulation of emotions can be derived via the assessment of parasympathetic and sympathetic processes of the autonomic nervous system (ANS) (for reviews, see Friedman, 2010; Kreibig, 2010). Respiratory sinus arrhythmia (RSA) and the cardiac preejection period (PEP) are the most commonly used measures of parasympathetic and sympathetic functioning, respectively, and have served to index emotion regulation in the study of STBs among community-based women (Tsypes et al., 2018).

Indeed, several theorists have posited that, among its various features, RSA also is a physiological marker of emotion regulation (e.g., Beauchaine & Thayer, 2015; Thayer & Lane, 2000). RSA mirrors the effect of the vagus nerve on cardiac inter-beat intervals. At rest, higher levels of RSA (strong vagal inputs) are associated with relaxation and signal better functional outcomes (Thayer, Hansen, Saus-Rose, & Johnsen, 2009). In response to stress and negative affective stimuli, decreased RSA, which reflects the lessening of vagal control over cardiac functioning, is commonly (but not always) considered normative, and facilitates the individual's ability to respond to environmental demands (for reviews see, Kreibig, 2010; Siegel et al., 2018). Neuroimaging studies have confirmed that RSA is associated with various brain regions that have been implicated in emotion regulation, including the amygdala and the ventromedial prefrontal cortices (for reviews, see Gianaros & Jennings, 2018; Thayer, Åhs, Fredrikson, Sollers III, & Wager, 2012).

Depression has been generally associated with low resting RSA and attenuated RSA reactivity to both stressful and affective stimuli (Bylsma, Salomon, Taylor-Clift, Morris, & Rottenberg, 2014; Kemp, Quintana, Quinn, Hopkinson, & Harris, 2014; Licht et al., 2008; Yaroslavsky, Rottenberg, & Kovacs, 2014; but see Hastings, Klimes-Dougan, Kendziora, Brand, & Zahn-Waxler, 2014). Low resting RSA and attenuated RSA reactivity to laboratory stressors

have also been observed among individuals with a history of STBs (Chang et al., 2013; Forkmann et al., 2016; James, Woody, Feurer, Kudinova, & Gibb, 2017; Rottenberg, Wilhelm, Gross, & Gotlib, 2002; Tsypes et al., 2018; Wilson et al., 2016). For example, compared to nonsuicidal women with a history of depression, those who also had attempted suicide displayed reduced RSA reactivity to a laboratory stressor (Wilson et al., 2016). Likewise, James et al. (2017) found that children with a history of suicidal ideation did not exhibit the typical RSA decrease during a (presumably stressful) parent-child interaction task. However, suicidal adolescents also have been reported to exhibit greater decrease in RSA than controls when responding to a sad film (Crowell et al., 2005) as well as laboratory stressors (Giletta et al., 2017; Kaufman et al., 2018). Thus, the literature on RSA and STBs is equivocal.

In contrast to RSA, PEP is an index of sympathetic functioning, which undergirds the processing of affective stimuli (Kreibig, 2010). PEP is the isovolumetric, ventricular contraction time prior to the ejection of blood into the aorta; shorter PEP indicates higher levels of beta-adrenergic sympathetic activation (Sherwood et al., 1990). In addition to providing an index of sympathetic arousal, PEP is believed to mirror cognitive effort (Gendolla, Wright, & Richter, 2012), a key process in many emotion regulation responses (Gotlib & Joormann, 2010). Compared to a resting state, PEP is shortened during stress exposure (Kelsey, 2012; Matthews, Gump, Block, & Allen, 1997; Salomon, Matthews, & Allen, 2000) but is not predictably affected by sadness-eliciting stimuli (e.g., for a review, see Kreibig et al., 2010; Stephens, Christie, & Friedman, 2010). Depression has been associated both with reduced and prolonged PEP responses to laboratory stressors (Salomon, Bylsma, White, Panaite, & Rottenberg, 2013; Salomon, Clift, Karlsdóttir, & Rottenberg, 2009; but see Light, Kothandapani, & Allen, 1998). Moreover, in a study of adolescents with a history of STBs and controls, there were no group

differences in PEP reactivity to a sad film (Crowell et al., 2005). Given the scant literature on PEP and emotion regulation in the context of suicidality, this index of ANS functioning is particularly worthy of attention.

In summary, emotion regulation is considered as a key to understanding STBs, which can be studied using physiological measures. However, most work in this area has focused on suicidal ideation or suicide attempts (e.g., Chang et al., 2013; Crowell et al., 2005; Giletta et al., 2017; James et al., 2017; Wilson et al., 2016), while the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; American Psychiatric Association, 2000) specifies four categories of STBs: recurrent *Thoughts of Death*, recurrent *Suicidal Ideation*, *Suicide Plan*, and *Suicide Attempt*. Therefore, in the present study, we sought to address the full range of STBs.

Our main goal was to examine whether STBs among previously depressed adolescents impact RSA and PEP reactivity to stressful and affective stimuli. An unsolvable puzzle served as the stressful stimulus; a sad film clip served as the affective stimulus. We hypothesized that: (1) adolescents with a history of depression and STBs will manifest less vagal withdrawal (less reduced RSA) during both tasks than adolescents with a history of depression but no history of STBs or controls; (2) adolescents with a history of depression and STBs will manifest higher levels of sympathetic activation (greater PEP shortening) in response to the unsolvable puzzle but not the sad film than will adolescents with a history of depression but no history of STBs or controls; and (3) among adolescents with a history of depression, severity of lifetime STBs will be negatively correlated with extent of vagal withdrawal (RSA decrease) during both tasks, and positively correlated with PEP shortening during the stressful task. Our hypotheses were informed by the literature showing that ANS responses are task-sensitive (i.e., stressful and affective stimuli both tend to elicit vagal withdrawal, but only a stressful task tends to elicit beta-

adrenergic sympathetic activation; e.g., Salomon et al., 2000; Stephens et al., 2010), that histories of STBs are associated with maladaptive physiological activity among ever-depressed individuals (e.g., Chang et al., 2013; Rottenberg et al., 2002), and that more severe forms of STBs among adolescents with a history of depression signal more extensive emotion regulation deficits (e.g., Tamás et al., 2007; Zlotnick et al., 1997). Our hypotheses also mirror the assumption that the effects of suicidal behaviors on physiological functioning are enduring, primarily trait-like, and above and beyond the consequences of depression. Therefore, to minimize the potential effects of depression states, we controlled for their presence at the time of the physiological assessments.

2. Method

2.1 Subjects

Our study included 224 adolescents (34.8% female) who had childhood onset depression and 175 healthy controls (34.9% female) who never had a history of any psychiatric disorder or STBs. The adolescents with a history of depression were a subset of a larger sample, which was recruited from 1997-2006 for a longitudinal study (Kiss et al., 2007; Tamás et al., 2007). The original study entry criteria included being 7- to 14- years of age; having a DSM-IV defined depressive disorder (see below); and being free of intellectual disability and major medical disorders. At the time of the present study, 177 of the 224 adolescents with a history of depression had lifetime STBs, while 47 did not.

Age of all subjects ranged from 11.20 to 19.08 years. As shown in Table 1, adolescents with a history of depression but no lifetime STBs were slightly younger than were adolescents with a history of depression and STBs, and controls were slightly younger than were all adolescents with a history of depression. Ever-depressed adolescents had the onset of their first

major depressive disorder (MDD) episode at 8.86 years of age (*SD* = 1.92 years), on average. At the time of the current study, 57.1% of ever-depressed adolescents had one MDD episode, 30.4% had two episodes, and 12.5% had three or more episodes; 192 (85.7%) were in full remission from their depressive disorder and 32 (14.3%) were in a current depressive episode (MDD and/or dysthymia). Altogether 17 (7.6%) adolescents with a history of depression had comorbid anxiety disorder. In addition, five adolescents with a history of depression and STBs and two adolescents with a history of depression but no lifetime STBs were taking psychiatric medication at the time of the assessments.

INSERT TABLE 1 ABOUT HERE

2.2 Recruitment and Diagnostic Assessment

The recruitment of subjects with a history of depression has been reported in detail and involved prescreening consecutive admissions to 23 separate child mental health sites in Hungary (Kiss et al., 2007; Tamás et al., 2007). Healthy controls were recruited from public elementary and secondary schools in the regions from which most of the depressed subjects were sampled. The study protocol was approved by the Institutional Review Board of the University of Pittsburgh and the Review Boards of the relevant entities in Hungary. Psychiatric caseness was established based on self- and parent-reported information during the semi-structured Interview Schedule for Children and Adolescents-Diagnostic version (ISCA-D). This standardized interview was administrated by trained clinicians in order to generate DSM-IV diagnoses. The ISCA-D is an extension of the ISCA (Sherrill & Kovacs, 2000) and has shown acceptable inter-rater reliability: κ ranges from .64 - .88 for current MDD symptoms with 80.0%

of the coefficients above .70 (Kiss et al., 2007). DSM-IV diagnoses were derived using a consensus diagnostic procedure (Maziade et al., 1992).

Information on suicidality was collected as part of the ISCA-D mood disorder module, which includes the four DSM-IV categories of STBs: recurrent Thoughts of Death was defined as repeatedly thinking about one's own death or wanting to die; recurrent Suicidal Ideation was defined as multiple instances of thinking about killing oneself but without specific plans; Suicide Plan was defined as having a specific plan or method to kill oneself; Suicide Attempt was defined as an executed behavior with some intent to kill oneself. Responses to these items were coded as binary (i.e., "yes" or "no"). If either Thoughts of Death or Suicide Ideation were endorsed, the other two items were rated; otherwise, they were skipped.

For the relevant statistical analyses, STBs for a given subject was defined as *the most severe form* of STBs reported across that subject's lifetime, ranging from recurrent thoughts of death to a suicide attempt. For example, if a subject had suicidal plans but never had suicide attempts, then the most severe lifetime STBs for the subject would be "Suicide Plan".

2.3 Physiological Recording and Apparatus

The instructions and laboratory tasks were presented on a computer screen using the E-prime 2.0 software (Psychology Software Tools, Pittsburgh, PA). Physiological signals were sampled online at 1000 Hz using a Mindware BioNex system and BioLab software (MindWare Technologies LTD, Gahanna, OH). Electrocardiography (ECG) and impedance cardiograph (ICG) were measured with disposable, pregelled stress-testing Ag/AgCl spot electrodes (CONMED Andover Medical, Haverhill, MA) with a modified Lead II configuration. Respiration was assessed by a respiration transducer placed around the subject's torso at the

abdominal level. RSA and PEP were analyzed by Mindware 3.0.21 software (MindWare Technologies LTD, Gahanna, OH), respectively.

2.4 Procedure

The experimental protocol included a series of tasks relevant to stress reactivity and emotion regulation. In the present article, we report physiological data obtained during a neutral film (baseline), a sad film clip, and an unsolvable puzzle task. Subjects were asked not to take medications for any allergy, cold, or asthma on the day of the experiment, and to abstain from caffeine, alcohol, and tobacco for two hours prior to participation. After consent was obtained, subjects were comfortably seated in the laboratory while electrodes and the respiratory transducer were attached.

To estimate baseline physiological functioning, subjects were instructed to sit still and watch a 180-second neutral film that depicted aquatic scenes (Jennings, Kamarck, Stewart, Eddy, & Johnson, 1992). Then, subjects responded to two tasks. One task was a 164-second sad film clip from the movie "The Champ," which depicts a boy's anguish over his father's death and has been widely used to induce sadness (Gross & Levenson, 1995; Rottenberg, Ray, & Gross, 2007). The other task involved puzzles: a pattern of letters was displayed on a computer screen and subjects were asked to move another set of letters to duplicate the displayed pattern. A 15-second solvable practice trial was followed by two 180-second trials one after the other, both of which were *unsolvable* (which was unbeknown to the subject). Unsolvable puzzles have been shown to induce psychological stress, helplessness, and frustration (Perry, Calkins, Nelson, Leerkes, & Marcovitch, 2012). The presentation order of the sad film and the unsolvable puzzle task was randomized. They were separated by an inter-task buffer period.

Subjects also provided affect ratings at baseline and after each task. Extent of self-rated dysphoria/sadness was the average rating of feeling sad and feeling blue. Extent of other negative emotions was the average rating of feeling anger, upset, nervous, and irritable. All emotions were rated on an eight-point Likert scale, ranging from "0" = none to "7" = very much.

2.5 Data Reduction

ECG data were inspected, and artifacts were corrected manually by trained raters. If 5% or more ECG signals in an epoch were influenced by artifacts, that epoch was excluded from analyses. RSA was assessed as the natural log-transformed values of high-frequency (0.12-0.40 Hz) heart rate variability spectral power, which was derived from inter-beat interval time series of ECG signals by a Mindware R-wave detection routine and then computed by a fast Fourier transformation. PEP was calculated as the time interval between the ECG Q-wave and the B-point on the wave form of the first-order derivative of ICG signals (dZ/dt; Sherwood et al., 1990). The B-point was detected by the max slope method and manually adjusted by trained raters. Physiological data were processed for the entire duration of each task. RSA decrease was calculated as: $\mathbf{-(RSA_{Task} - RSA_{Baseline})}$; PEP shortening was calculated as: $\mathbf{-(PEP_{Task} - PEP_{Baseline})}$.

2.6 Analysis Approach

Two separate 2 (Task: baseline vs. task) × 3 (Group: ever-depressed adolescents with lifetime STBs, ever-depressed adolescents with no lifetime STBs, and controls) repeated measures analyses of covariance (rANCOVA) served to examine the association of the unsolvable puzzle and sad film and each ANS measure, as we were primarily interested in reactivity to the two different tasks. Physiological scores for at least two epochs (baseline and a task) were required for a subject to be included in the rANCOVA. Pairwise deletion was used to

deal with missing data. In the analyses, 399 (100%) subjects had valid RSA scores and 396 (99.2%) subjects had valid PEP scores at the baseline; 395 (99.0%) subjects had valid RSA scores and 390 (97.7%) subjects had valid PEP scores for the unsolvable puzzle task; 396 (99.2%) subjects had valid RSA scores and 391 (98.0%) subjects had valid PEP scores for the sad film. The three groups did not differ in missing data (chi-square tests: *p*s > 0.34).

In order to examine group differences in RSA reactivity (*Hypothesis 1*), RSA scores were submitted to rANCOVA, controlling for age, sex, standardized body mass index (BMI), smoking status, current depressive spectrum and current anxiety disorders. Similarly, to test *Hypothesis 2*, PEP scores were submitted to rANCOVA, controlling for the above noted set of covariates. Contrasts were planned to probe interactions by comparing each pair of the three groups. To test *Hypothesis 3* referring to adolescents with a history of depression, we computed one-tailed nonparametric Spearman's rank order correlations between ANS reactivity (i.e., RSA decrease and PEP shortening during the tasks) and severity of STBs. There were five levels of lifetime STBs ranging from no STBs (lowest level) to Suicide Attempt (highest level).

3. Results

3.1 Descriptive Characteristics

The three groups of subjects did not differ in sex distribution, $\chi^2 = 0.016$, $p = 0.99$ but adolescents with a history of depression and STBs were older than were controls, $F(2, 298) = 11.2$, $p < 0.001$. There was a marginal group difference in BMI, $F(2, 298) = 2.99$, $p = 0.051$. As expected, relative to controls, adolescents with a history of depression were more likely to have a current depressive episode, $\chi^2 = 32.2$, $p < 0.001$, an anxiety disorder, $\chi^2 = 15.2$, $p < 0.001$, and be smokers, $\chi^2 = 81.2$, $p < 0.001$, (see Table 1). Additionally, the two groups of ever-depressed

adolescents did not differ in the ratio of subjects taking psychiatric medication, $\chi^2 = 0.25$, $p = 0.62$.

INSERT FIGURE 1 ABOUT HERE

We also examined baseline RSA and PEP values (see Figure 1). We found that the three groups of subjects did not differ on either variable: RSA, $F(2, 390) = 2.09$, $p = 0.13$ and PEP, $F(2, 387) = 0.06$, $p = 0.95$.

3.2 Affect Ratings

We compared pre versus post task affect ratings as a manipulation check. As expected, exposure to the sad film increased the rating of sadness from 0.42 (*SD* = 0.90) at baseline to 1.15 (*SD* = 1.18), $F(1, 398) = 147.7$, $p < 0.001$, $\eta_p^2 = 0.271$. Likewise, exposure to the unsolvable puzzle increased the level of other negative emotions (angry, upset, nervous, and irritable) from 0.43 (*SD* = 0.63) at baseline to 0.78 (*SD* = 0.97), $F(1, 398) = 70.07$, $p < 0.001$, $\eta_p^2 = 0.150$.

We also conducted rANCOVA (controlling for current depressive spectrum and anxiety disorders) to explore group differences in affect ratings. Sadness ratings showed a task-by-group interaction after the sad film, $F(2, 394) = 11.65$, $p < 0.001$, $\eta_p^2 = 0.056$. Specifically, controls evidenced a greater increase in sadness after the sad film than did the two groups of adolescents with a history of depression, while the latter two groups did not differ from one another. The intensity of other negative emotions after the puzzle task was similar across the three subject groups, $F(2, 394) = 1.20$, $p = 0.30$.

3.3 RSA Reactivity

2 (Task) × 3 (Group) rANCOVA served to test group differences in RSA change during the **stressful unsolvable puzzle**. Results showed a trend toward a main effect of task, $F(1, 386) = 3.03$, $p = 0.083$ and a significant interaction between task and group, $F(2, 386) = 3.26$, $p = 0.04$, $\eta_p^2 = 0.017$. Planned contrasts revealed that the task-by-group interaction was driven by a notable RSA decrease among controls, but not among adolescents with a history of depression and STBs, $F(1, 341) = 7.23$, $p = 0.01$, $\eta_p^2 = 0.021$. In fact, RSA did not decrease at all in the latter group, $t(175) = 0.22$, $p = 0.83$.

Group differences in RSA reactivity to the **sad film** were also tested by a 2 × 3 rANCOVA. The results revealed no main effect of task, $F(1, 387) = 0.77$, $p = 0.38$ nor a sad film task-by-group interaction, $F(2, 387) = 0.16$, $p = 0.85$. Thus, the sad film elicited similar RSA responses across the three groups of subjects (see Figure 1).

3.4 PEP Reactivity

PEP values at baseline and during the **unsolvable puzzle** were subjected to a 2 × 3 rANCOVA. Results indicated no main effect of task, $F(1, 381) = 1.32$, $p = 0.25$, but a significant task-by-group interaction, $F(1, 381) = 3.90$, $p = 0.02$, $\eta_p^2 = 0.020$. Probing this interaction revealed less attenuation of PEP among ever-depressed adolescents with no lifetime STBs than ever-depressed adolescents with lifetime STBs, $F(1, 212) = 5.82$, $p = 0.02$, $\eta_p^2 = 0.027$ and controls, $F(1, 207) = 4.50$, $p = 0.04$, $\eta_p^2 = 0.021$. However, PEP responses were similar among ever-depressed adolescents with lifetime STBs and controls, $F(1, 337) = 0.73$, $p = 0.39$.

Group differences in PEP reactivity to the **sad film** were also tested by a 2 × 3 rANCOVA. The results revealed no main effect of task, $F(1, 382) = 1.73$, $p = 0.19$ nor a task-by-group interaction, $F(1, 382) = 2.55$, $p = 0.08$ (Figure 1).[1]

3.5 Relation between ANS Reactivity and Severity of SBTs

Severity of lifetime STBs among adolescents with a history of depression was positively related to PEP shortening during the stressful unsolvable puzzles (Spearman's $r = 0.16$, $p = 0.01$; see Figure 2). Severity of lifetime STBs was likewise positively related to changes in PEP values during the sad film, $r = 0.22$, $p = 0.001$. The correlation coefficients remained significant after Bonferroni correction. However, severity of lifetime STBs did not correlate with RSA reactivity to either experimental task, ps > 0.79.

INSERT FIGURE 2 ABOUT HERE

4. Discussion

The goal of our study was to examine whether STB histories in the context of depression are associated with atypical autonomic responses to stressful and affective stimuli. Given that such stimuli are prevalent in daily life, appropriate physiological responses are important in order to facilitate adaptive functioning. On the other hand, atypical physiological responding, which may signal emotion dysregulation, could represent either a risk factor for, or a consequence ("scar") of histories of STBs, and contribute to the functional difficulties of such individuals.

To achieve our study's goal, we proposed three hypotheses, which were partially supported. When facing a stressful task, adolescents with a history of depression and STBs did not show RSA decrease (i.e., there was an absence of vagal withdrawal) but displayed greater PEP shortening relative to ever-depressed adolescents with no lifetime STBs (i.e., heightened sympathetic activation). However, when facing an affective stimulus, the three groups of subjects did not differ in RSA or PEP reactivity. Moreover, among the youths with a history of depression, greater PEP shortening, but not RSA decrease, was positively correlated with

severity of lifetime STBs. In other words, among previously depressed adolescents, the highest levels of sympathetic activation during the stressful task were among those who had had the most serious forms of STBs (i.e., suicide plans or attempts).

Our results are in line with prior reports of blunted RSA reactivity to laboratory stressors among subjects with a history of STBs (James et al., 2017; Wilson et al., 2016) and extend the findings to STBs in the context of depressive disorders. Recall that the normative response to stress is reduced RSA, which facilitates a variety of physiological processes, allowing the person to respond to environmental demands. Blunted RSA reactivity to stress has been interpreted as attenuated physiological regulation (James et al., 2017; Wilson et al., 2016), which fails to prepare the person for optimally managing the task or challenge that has arisen. This finding coheres with suicidal individuals' difficulties in problem solving and supports the conceptual and empirical link between impaired emotion regulation skills and suicidal behaviors (Pollock & Williams, 2004; Schotte & Clum, 1987).

Blunted RSA reactivity could be a "scar," reflecting the physiological consequences of past STBs and/or depression. Indeed, our hypotheses were based on the assumption that the effects of suicidal behaviors on physiological functioning are enduring, or trait-like, and are beyond the effects of depression itself. However, atypical RSA functioning may have predated STB histories in our cohorts, which would render that physiological index a bona fide risk factor. Such a possibility could be explored in future longitudinal investigations.

Our findings on RSA reactivity seem inconsistent with results from two earlier studies: Crowell et al. (2005) reported that female self-harming adolescents had elevated RSA reactivity to a sad film compared to controls, while Giletta et al. (2017) found that high levels of RSA reactivity to a stressor predicted suicidal ideation 9 months later. The discrepancy between the

present findings and the just noted reports is likely to reflect substantial differences in sample characteristics, definitions of STBs, and data analytic approaches. First, all suicidal adolescents in our study had been clinically ascertained and were previously depressed. In contrast, suicidal subjects in the other studies either did not receive a psychiatric diagnostic assessment (Crowell et al., 2005), or included community-based subjects (Giletta et al., 2017). Second, Crowell et al.'s (2005) sample included self-harming nonsuicidal subjects along with suicidal ones, while Giletta et al. (2017) studied ideators who could have qualified by a single episode of suicidal ideation. Last, Crowell et al. (2005) examined physiological data in small epochs, while Giletta et al. (2017) used standardized residual (not raw) scores to analyze physiological data. Further, unlike in our analyses, these two studies' data analytic approaches did not directly report on actual RSA augmentation or reduction during the entire experimental task.

We also found that, in response to the stressful stimulus, adolescents with a history of depression and STBs displayed higher levels of sympathetic activation (greater PEP shortening) than did their nonsuicidal peers, but did not differ from normal controls. Recall that PEP also has been considered to reflect cognitive effort (Gendolla et al., 2012), a key component of emotion regulation. Given that the effort expended by adolescents with a history of depression and STBs to solve the task was comparable to the effort displayed by normal controls, the finding may reflect these suicidal adolescents' attempt to compensate for their blunted contemporaneous parasympathetic functioning. Similar presumably compensatory processes have been reported among young offspring at high risk for familial depression, who performed as well as controls did on an experimental task, but required more neural resources to do so (Pérez-Edgar, Fox, Cohn, & Kovacs, 2006).

The present study is the first to report that the extent of sympathetic activation in response to experimental probes indexes severity of lifetime STBs. According to some current models of the suicidal process, a better understanding of the transition from ideation to attempts is critical to prevention efforts (Klonsky, May, & Saffer, 2016; Van Orden et al., 2010). Our findings suggest that excessive sympathetic activation in response to environmental triggers (but not vagal reactivity) may serve as one physiological mechanism, which facilitates the progression from milder to more severe STBs in previously depressed adolescents. While this novel finding requires replication, it suggests that current models of the suicidal process may benefit from including physiological dimensions.

It is notable that we failed to find group differences in ANS reactivity to the sad stimulus. However, the results concerning PEP are in line with some prior studies of sadness induction, which used film clips and reported unchanged PEP (Stephens et al., 2010): it is likely to mirror that viewing a film clip is a passive act requiring little effort. The lack of group differences in RSA reactivity suggests that, unlike self-reported subjective sadness (e.g., Nock et al., 2008; You et al., 2012), some physiological reactivity may be more likely to be triggered by frustration and helplessness than sadness. Consistent with this notion, Csorba et al. (2003) reported that hopelessness differentiated suicidal depressed adolescents from their nonsuicidal peers. However, the shorter length of the sadness induction, as compared to the unsolvable puzzle task, may have contributed to the null results. In other words, 180 seconds of a sad film may be too short to induce group differences in physiological responses. Future studies using tasks with equal lengths should consider this potential confounding effect. All in all, the findings suggest that attempts to use physiological reactivity as a risk marker of STBs in the context of depression should focus on potentially stressful and cognitively demanding tasks.

An unexpected finding was that the sad film induced less subjective sadness among adolescents with a history of depression than it did among controls (based on affect self-ratings). Such blunted reactivity is partly consistent with the concept of emotion context insensitivity, which is believed to characterize depression (Rottenberg, Gross, & Gotlib, 2005; Rottenberg, 2017). Evidence of blunted reactions to sadness but not to frustration provocation suggests that "emotion insensitivity" in the presence of depression history may be specific to sadness-related stimuli. Additionally, subjective ratings and physiological responses to the sad film were not in concert. Lack of coherence between subjective experience and physiologic processes is not well understood, although greater coherence between self-reported affect and contemporaneous physiology has been linked to greater well-being (Brown et al., in press).

Given that several physiological indices of emotion regulation were atypical among our subjects with a history of depression (compared to controls), the findings also have clinical implications. More specifically, difficulties in emotion regulation among youths with depression may be maintained by the underlying physiology and compromise the ability to manage stresses. Because emotion regulatory behavior is modifiable, its improvement therefore should be part of intervention efforts for STBs in the younger ages.

Our findings need to be evaluated in light of several design weaknesses, the most important of which is the cross-sectional nature of the study, which precluded an assessment of atypical physiological reactivity as a risk factor for STBs. Further, the absence of a sample with STBs but no depression history made it difficult to fully disentangle the effects of depression and STBs on physiological functioning. Given that juvenile-onset depression has been associated with adverse early experiences, which can influence physiology, it could be argued that our results reflect such early experiences rather than STBs. But that is unlikely to be the case because

previously depressed youths with STBs in our study differed from those with a history of depression but no lifetime STBs on several indices of reactivity. And, as noted above, the unequal lengths of tasks may have contributed to the null findings regarding the sad film. Finally, future studies may benefit from using more sophisticated data modeling approaches (e.g., latent growth curve analyses). However, our study also has several positive features, including comprehensive diagnostic evaluation of subjects, assessment of the entire DSM-specified range of STBs, a focus on multiple physiological systems, a large sample, and conceptually meaningful laboratory tasks. The results therefore add to the relatively scant literature on physiological correlates of STBs and may contribute to more comprehensive interventions for individuals with STBs.

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Footnote

1. To test for quadratic effects in the association between group and ANS reactivity, we regressed the square of mean-centered ΔRSA and ΔPEP during laboratory tasks on group in four separate models, controlling for the same set of covariates as in the main analyses. Results showed no significant group differences in quadratic functions of ANS reactivity, with Fs < 1.06, ps > 0.35.

Figure Captions

Figure 1. Mean RSA (upper panel) and PEP (lower panel) during tasks. Means are adjusted for sex, age, standardized BMI (*Z*-score), smoking status, current depressive spectrum episode, and current anxiety disorder. STBs = Suicidal thoughts and behaviors; C.I. = Confidence interval.

Figure 2. Mean PEP shortening during the unsolvable puzzle task (= $PEP_{Baseline} - PEP_{Unsovable\ Puzzle}$) and severity of suicidal thoughts and behaviors (STBs) among adolescents with a history of depression. C.I. = Confidence interval.

Table 1. *Demographic and Clinical Characteristics of Groups*

Variable	Adolescents with lifetime depression and STBs (*n* = 177)	Adolescents with lifetime depression but no STBs (*n* = 47)	Control adolescents (*n* = 175)
Female (*n*, %)	62 (35.0%)	16 (34.0%)	61 (34.9%)
Age (years; *SD*)	17.1 (1.4)	16.8 (1.5)	16.2 (2.1)
BMI (*SD*)	21.8 (4.4)	23.5 (5.7)	20.9 (3.5)
Smoking Status (*n*, %)			
Never	85 (48.0%)	33 (70.2%)	159 (90.9%)
Occasion	25 (14.1%)	4 (8.5%)	11 (6.3%)
Regular	67 (37.9%)	10 (21.3%)	5 (2.8%)
Current Depressive Spectrum Episode (*n*, %)	29 (16.4%)	3 (6.4%)	0 (0%)
Current Anxiety Disorder (*n*, %)	12 (6.8%)	5 (10.6%)	0 (0%)

Note: STBs = Suicidal thoughts and behaviors; BMI = Body mass index; "Depressive Spectrum" includes major depressive disorder and dysthymia.

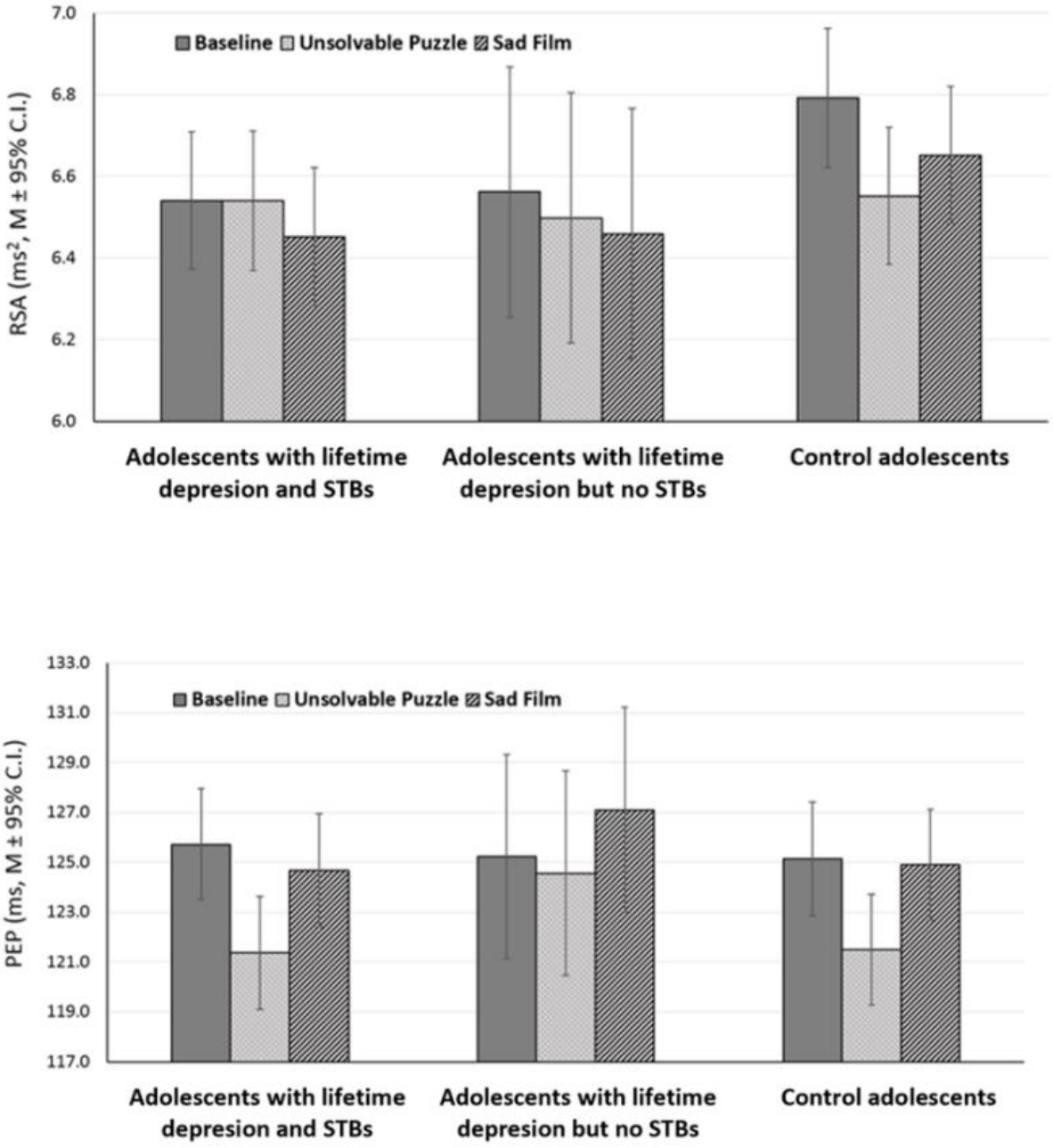

Figure 1. Mean RSA (upper panel) and PEP (lower panel) during tasks. Means are adjusted for sex, age, standardized BMI (*Z*-score), smoking status, current depressive spectrum episode, and current anxiety disorder. STBs = Suicidal thoughts and behaviors; C.I. = Confidence interval.

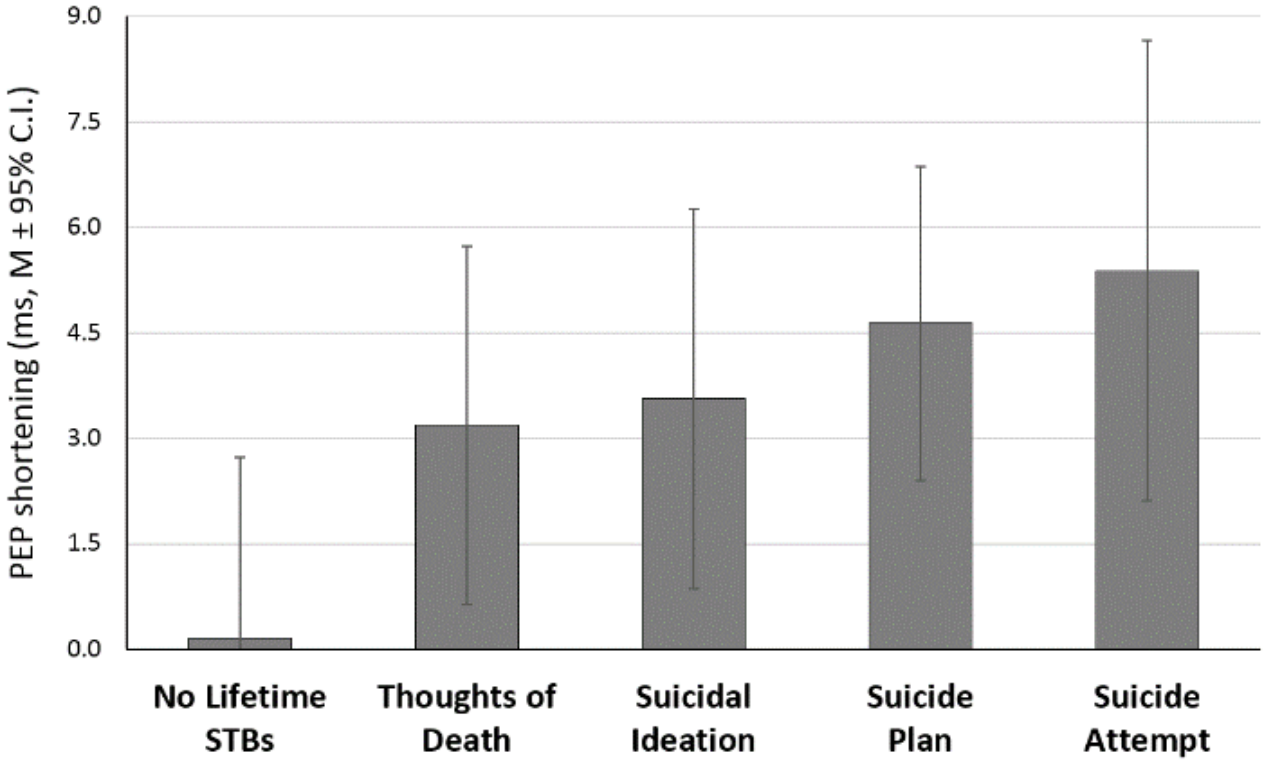

Figure 2. Mean PEP shortening during the unsolvable puzzle task (= $PEP_{Baseline} - PEP_{Unsovable\ Puzzle}$) and severity of suicidal thoughts and behaviors (STBs) among adolescents with a history of depression. C.I. = Confidence interval.