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Research paper

Cognitive inflexibility and suicidal ideation among adolescents following hospitalization: The moderating role of life stress

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ABSTRACT

Background: Cognitive inflexibility has recently been investigated as potential vulnerability factor for suicidal ideation (SI), but the context in which it may convey risk is unclear. Life stress has also been reliably associated with SI among adolescents, and following a stress-diathesis model, may be a factor that moderates the relationship between cognitive inflexibility and SI.

Methods: Psychiatrically hospitalized adolescents ($N = 259$) at high risk for future SI were followed for 18 months after discharge. Interviews assessing life stress and SI and a neurocognitive task assessing cognitive inflexibility were conducted at six- and 12-months. SI was also assessed at 18-month post-discharge. Linear mixed models were used to determine the moderating effect of stress on the relationship between cognitive inflexibility and SI, accounting for relevant clinical and demographic covariates.

Results: Chronic stress moderated the association between cognitive inflexibility and SI, with a stronger association found among youth with greater levels compared to lower levels of chronic stress. This finding was maintained after statistically adjusting for depressive symptoms and relevant demographic covariates. No prospective associations between cognitive inflexibility, life stress, and SI were found.

Limitations: SI was measured at 6-month intervals, precluding evaluation of the relationship on a more proximal timescale.

Conclusions: Cognitively inflexible adolescents under conditions of high chronic stress are more likely to experience increased SI severity, supporting a cognitive inflexibility stress-diathesis model of SI in adolescents. The findings highlight the importance of assessing these modifiable factors among adolescents at a high risk for SI.

1. Introduction

Death by suicide, particularly for youth, has been increasing markedly since 2007 (Miron et al., 2019). Although correlates for suicidal ideation (SI), a precursor and reliable predictor of suicide death, are well researched, rates of SI and related emergency department visits among adolescents have continued to rise (Ivey-Stephenson et al., 2020; Ribeiro et al., 2016). Recent research investigating neurocognitive functioning in risk for SI suggest cognitive inflexibility, or deficits in cognitive flexibility, as a particular vulnerability. Additionally, the moderating role of life stress, within a stress-diathesis model of suicide, may be a particularly important factor to consider. As such, the current study examines the moderating role of life stress on the association between cognitive inflexibility and SI among adolescents.

Cognitive flexibility refers to the ability to adjust to feedback from the environment and selectively switch between mental processes in the service of generating appropriate behavioral responses (Armbruster et al., 2012; Dajani and Uddin, 2017). Encompassing multiple separate processes such as *inhibiting* inappropriate goals and *shifting sets* to respond to changing environmental demands (Diamond, 2013; Miyake et al., 2000), cognitive inflexibility has been implicated as a transdiagnostic, neurocognitive risk factor related to a variety of

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psychopathological disorders (Kim et al., 2012; Niendam et al., 2012). Cognitive flexibility is also an essential executive function necessary for problem-solving, which itself has been shown in previous studies to be associated with suicidal behavior in adolescents (for a review, see Speckens and Hawton, 2005).

The literature directly investigating cognitive inflexibility and SI, however, has been relatively limited. Neurobehavioral indices of cognitive inflexibility have only recently been examined in relationship to SI, and most studies to date have been conducted with adult samples (Bredemeier and Miller, 2015). Broadly, however, the current evidence suggests that cognitive inflexibility is related to SI (Bredemeier and Miller, 2015). In the two investigations of the association between cognitive inflexibility and suicidal ideation and behavior among adolescents, results were mixed (MacPherson et al., 2022; Ruch et al., 2020). In one study (MacPherson et al., 2022), adolescents with histories of suicide attempt demonstrated greater cognitive inflexibility relative to peers with no history of psychiatric illness. However, adolescents with histories of suicidal ideation only did not differ significantly in terms of cognitive inflexibility relative to peers recruited from the community with no history of mental illness and relative to individuals with a history of suicide attempt. In another study (Ruch et al., 2020), no significant differences among adolescents with a history of suicide attempt, suicidal ideation only, or depressive symptoms but no suicidality were found.

Importantly, these studies both employed cross-sectional analyses of cognitive flexibility and SI. Additionally, MacPherson et al. (2022) compared psychiatric inpatients with SI to peers recruited from the general community with no history of psychiatric conditions. This complicates interpretation of any positive findings insofar as it is not possible to determine whether they are due to suicidal thoughts and behaviors rather than the psychiatric comorbidity found in psychiatric inpatients when compared to adolescents with no psychiatric illness, especially given that cognitive flexibility has been implicated in other psychiatric conditions prevalent on inpatient units, such as depression (Heinzel et al., 2010). Although Ruch et al. (2020) included a psychiatric control group recruited from the same patient population as participants with a history of suicidal thoughts and behaviors, the suicidal groups were based on lifetime history of suicidal thoughts and behaviors, meaning in some cases, occurrence of suicidal ideation may have temporally preceded assessment of cognitive flexibility by a substantial length of time, which limits inferences regarding cognitive inflexibility as a risk factor for future SI.

In the only prospective study examining these issues, cognitive inflexibility among young adults, as indexed by the Wisconsin Card Sort Test, predicted later SI (Miranda et al., 2012; Miranda et al., 2013). However, many existing studies investigating cognitive inflexibility and SI, including the only prospective studies, have utilized community samples consisting of college students and young adults (Cha et al., 2019). Despite the importance of prefrontal cortical development in adolescence, which is necessary for executive functioning processes such as cognitive flexibility, and the time varying nature of SI, no studies have investigated cognitive inflexibility among adolescents in relation to SI over time. As such, generalization of longitudinal findings with adults to youth cannot be assumed.

SI is a complex, multidetermined phenomenon, and no one predictor is sufficient for predicting its occurrence. Consequently, not every adolescent demonstrating cognitive inflexibility will experience SI. The stress-diathesis model of suicidal behavior provides a framework through which we may begin to understand *how* cognitive inflexibility may represent a vulnerability for SI among adolescents. It posits that the development of SI requires both a diathesis, or trait-like vulnerability that predisposes an individual to SI, *and* conditions of stress (van Heeringen, 2012; Mann, 2003). It is possible that while cognitive inflexibility may represent a diathesis, life stress may be a necessary condition through which this vulnerability affects risk for suicidal thoughts and behaviors (STBs). Indeed, the relationship between cognitive inflexibility and life stress suggests an interactive effect that leads to pertinent clinical outcomes. For example, cognitive flexibility has been shown to be related to resilience to negative life events and stress (Genet and Siemer, 2011) and acute stress has been found to affect core executive functions such as cognitive inflexibility (Shields et al., 2016). Additionally, a prospective study found that task switching, a component of cognitive flexibility, interacted with high levels of stress to predict rumination, suggesting cognitive inflexibility as a vulnerability factor for increased perseverative negative thinking *under conditions of stress* (De Lissnyder et al., 2012). Thus, investigating cognitive inflexibility as a potential diathesis leading to risk for SI under conditions of high stress is critical to the identification of suicide risk among adolescents.

In evaluating cognitive inflexibility and life stress in a stress-diathesis model of suicide, several important methodological considerations should be mentioned. Although life stress is largely considered a reliable predictor of SI among adolescents (Liu and Miller, 2014), the vast majority of studies feature self-report measurement of stressful life events, which may confound psychopathology (e.g., depression) or associated characteristics (e.g., negative attentional bias) with the life stress (Hammen, 2005; Monroe, 2008). Self-report measures of life stress are likely to inflate estimates of the strength of the association between this construct and suicide outcomes. Contextual threat interviews utilize systemic identification and probing within several relevant life domains to assess chronic stress, as well as a separate systemic process for identifying the presence of event occurrences and associated, relevant contextual information. Chronic stress refers to the pervasive aspects of one's social or physical environment, involving deprivation or disadvantage, that represent an ongoing threat and challenge to an individual (Compas, 1987). Episodic stress represents discrete, stressful occurrences that are marked by threat and challenge to an individual outside of the context of a typical social or physical environment. These semi-structured interviews are unique in their assessment of both chronic and episodic stress, and are used in less than 5 % of the studies in this area (Liu and Miller, 2014). They provide a more rigorous evaluation of life stress in relation to suicide outcomes, dating and recall of life events, and are less affected by mood congruent biases (Mcquaid et al., 2000; Simons et al., 1993). Research utilizing this methodology is necessary for an accurate assessment of life stress in relation to SI.

The current study aims to address the aforementioned limitations of the existing literature. Specifically, it provides the first examination of cognitive inflexibility, measured using a neurocognitive assessment, as it relates to SI among adolescents over time. Further, the assessment of life stress as a moderator of the association between cognitive inflexibility and SI integrates the separate literatures on executive function and life stress within a stress-diathesis conceptual framework to predict SI in this critical developmental period. Finally, the literature on cognitive flexibility and life stress in relation to SI largely utilizes community samples in cross-sectional designs, precluding an examination of how these constructs relate to the specificity of SI relative to more general psychopathology. In the current study, we investigate the moderating effect of life stress on the relationship between cognitive inflexibility and SI in a clinically acute sample of adolescents in a longitudinal, multi-wave design. That is, we examine the concurrent and prospective main and interactive effects of life stress and cognitive inflexibility as it relates to SI in a clinically acute sample of adolescents following discharge from psychiatric hospitalization. To address methodological limitations pervasive in the literature, the current study utilizes a contextual threat interview (Hammen and Brennan, 2001; Monroe, 2008) which is considered “gold standard” because of the rigorous interview-based methodology, validity, and the ability to assess both chronic stress and episodic stress, as well as a behavioral measure of cognitive inflexibility in a longitudinal design.

2. Method

2.1. Participants

Participants were 259 (M_{age} = 14.97, SD = 1.41, 73 % assigned female at birth) adolescents between the ages of 12 and 18 years recruited from an inpatient psychiatric facility in the northeastern United States. They were enrolled in either a naturalistic longitudinal study (n = 180) or a randomized controlled trial (RCT) for adolescent suicide (n = 79). Eligibility screening was conducted by trained masters and doctoral level clinicians and post baccalaureate research assistants following review of electronic health records and discussion with treatment teams. Eligibility criteria differed slightly among studies, although the recruitment procedure, assessment battery, and patient population were identical. Inclusion criteria for the naturalistic longitudinal study included admission to a psychiatric inpatient facility within one month of consent and English fluency. Participants were eligible for the RCT, which investigated the efficacy of an intervention designed for high-risk, suicidal adolescents, if the primary reason for hospitalization was suicidal thoughts or behaviors and they met criteria for major depressive disorder (MDD), dysthymia, or a mood disorder not otherwise specified. The primary reason for psychiatric hospitalization was determined through chart review. Additionally, participants must have experienced one of the following to be eligible for the RCT: 1) non-suicidal self-injury (NSSI) on at least 5 occasions in the past 6 months, 2) a suicide attempt, or 3) recurrent substance abuse. Thus, inclusion criteria were more restrictive for the RCT. Exclusion criteria for both studies included an IQ below 80, measured by the Wechsler Abbreviated Scale of Intelligence, and acute psychosis or Pervasive Developmental Disorder. Additional exclusion criteria for the RCT were a primary diagnosis of either obsessive-compulsive disorder or an eating disorder. All diagnoses necessary for assessing eligibility were determined based on administration of the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS-PL). Eligible participants and families provided informed consent and completed initial screening measures to determine final eligibility.

Of note, participants in the RCT treatment condition did not differ from those in its control condition at any follow-up assessment in terms of suicide attempts, NSSI, or rehospitalization (Esposito-Smythers et al., 2019). Regarding differences between samples on key study variables at baseline, participants in the clinical trial had greater depressive symptoms [$t(257) = 3.02$, $p = .003$] and greater chronic stress [$t(257) = 2.07$, $p = .040$] than participants in the naturalistic longitudinal study. They did not differ in SI [$t(257) = 1.19$, $p = .235$], cognitive flexibility [$t(251) = 0.77$, $p = .442$], and episodic life stress [$t(255) = 0.53$, $p = .599$].

2.2. Procedure

Baseline measures were administered during index hospitalization. Potentially eligible participants and their families were approached, and those willing to participate provided informed consent. Rhode Island Hospital institutional review board study approval was obtained for the study. Follow-ups occurred six-, 12-, and 18-months following discharge. Measures of SI, depressive symptoms, life stress, and cognitive flexibility were administered at baseline, six-, and 12-month follow-ups. Of the 259 enrolled participants, retention rates were: 88.4 % at six months, 88.0 % at 12-months, and 87.2 % at 18-months. A series of independent sample t-tests and χ^2analyses were conducted to assess for attrition bias. No significant baseline differences were found between individuals who completed their 18 month assessment and those who did not, with the exception of baseline IED errors, with participants with missing data at 18-month follow-up exhibiting less cognitive inflexibility at baseline [$t(66.36) = 2.00$, $p = .05$].

2.3. Measures

2.3.1. Suicidal ideation

SI was assessed with the Suicidal Ideation Questionnaire – Junior (SIQ-JR; Reynolds, 1988). The SIQ-JR is a 15-item measure assessing SI over the past 30 days on a 7-point Likert scale from 0 (*"I've never had this thought"*) to 6 (*"Almost every day"*). The SIQ-JR has demonstrated adequate concurrent and construct validity and good internal consistency with a clinical sample of adolescents (Reynolds and Mazza, 1999). In the current study, internal consistency was high across timepoints (αs = 0.93–0.96).

2.3.2. Depressive symptoms

Depressive symptoms were measured using the Children's Depression Inventory 2nd Edition (CDI-2; Kovacs, 2011), a 28-item measure with response options ranging from 0 to 2. The CDI-2 demonstrated excellent internal consistency in the current sample (α = 0.91). To avoid confounding depression with the outcome (SI), the SI question was omitted from the total CDI-2 score for the current study.

2.3.3. Life stress

Life stress were measured using the UCLA Life Stress Interview (LSI), modified for use with adolescents (Hammen, 2005; Hammen and Brennan, 2001). The LSI is a psychometrically valid, semi-structured interview that was used in the currents study to assess chronic and episodic life stressful that occurred in the six months prior to interview administration (Hammen, 2016; Hammen and Brennan, 2001). The LSI utilizes the contextual threat method of life stress assessment (Brown and Harris, 1978), which emphasizes the impact of the context-dependent nature of life stress on mental health. The LSI includes separate modules for chronic stress across multiple domains, as well as episodic stress (or stressful life events). In current conceptualizations of chronic and episodic stress in the life stress literature(Hammen, 2005), episodic stress is defined as stressful events that have a temporally delimited occurrences with clear onset and offset, in contrast to chronic stress, which persists for longer periods of time and may dissipate more gradually.

For the interview modules assessing chronic stress over the past six months or since previous assessment period, adolescents were asked to provide contextual information on functioning and stress within a variety of domains. Information was collected about family relationships, peer relationships, relationship with their closest friend, romantic relationships, academic functioning, school behavioral functioning, their own physical health, and their families' physical and emotional health. Specific prompts and questions assessing the presence of stress within those domains were used to determine severity of chronic stress. Following the interview, the interviewer rated each domain on a scale of 1 to 5, with half point increments, where 1 indicated presence of exceptional relationships or no chronic stress, and 5 indicated severe chronic stress (e.g., abusive relationship, school expulsion). Scores were calculated by summing the score for each domain to assess for overall chronic stress.

In the episodic stress module, information on the nature of the event, context, and date were collected by trained interviewers. Initial probes, temporal anchors, and monthly calendars were provided to aid accurate recall of event dates. After the LSI was administered, the interviewer presented the narrative form of each life event, including the context surrounding the event, to a team of three or more trained coders who were blind to the participant's psychopathology and subjective reaction to each event. This team rated the impact of each event on a scale of 1 (*no significant threat or negative impact*) to 5 (*maximal negative impact or threat*) based on relevant contextual factors, such as the consequences, expectedness, and duration. For the current analysis, the objective impact scores for each stressful life event were summed for each participant to index overall episodic stress.

2.3.4. Cognitive inflexibility

Cognitive inflexibility was measured using the Cambridge Neuropsychological Testing Automated Battery (CANTAB) intra-extra dimensional (IED) set shift task (Cambridge Cognition, 2021). This measure was modeled after the Wisconsin Card Sorting Task, and has demonstrated excellent construct validity in a sample of adolescent psychiatric patients (MacPherson et al., 2022; Rahmani et al., 2021). In this task, participants were presented with two distinct shapes and instructed to choose between them, using trial-and-error learning to determine the correct rule. Once the participant made six consecutive correct responses, the next stage began, and the rule changed. This task contained nine stages with distinct "rewarded" stimuli. The initial stages presented simple, one-dimensional, pink shapes. Next, white lines overlaid the pink shape to create compound stimuli. To establish set formation, test shifts in stages one to seven were intra-dimensional (ID), with only the pink shapes being relevant. These stages assessed generalization of learning. The critical extra-dimensional (ED) shift occurred at stage eight when the white lines, previously irrelevant stimuli, became relevant, and thus attentional set shifting was required for adaptive response. In the following, final stage, the rule reverts. The number of perseverative errors following the ED shift was used as an index of cognitive inflexibility in the current study.

3. Data analysis

Linear mixed models (LMM) with a first order autoregressive (AR1) covariance structure were used to examine the association between ED shift errors, life stress, and SI. An AR1 covariance structure was selected to account for correlations between responses across time (Bolger and Laurenceau, 2013). Time was coded as a categorical value representing each separate timepoint (i.e., baseline = 1, six month = 2, 12-month = 3). Separate models were conducted to examine the effects of chronic and episodic life stress. We first tested for the main and interactive effects of each stress variable and ED shift errors on SI. Next, where a significant main effect or interactive effect was observed, we examined whether these effects were maintained when statistically adjusting for the influence of relevant demographic and clinical characteristics added to the model as covariates, including age, sex, minoritized status (white = 0; racially/ethnically minoritized = 1), time, and depressive symptoms at baseline. To assess for the prospective relationship between ED shift errors, life stress, their interactive effect and SI, a lead variable was created for SI (time + 1). Additional linear mixed models with an AR1 covariance structure were conducted to examine the association between ED shift errors, life stress, and subsequent timepoint SI. Separate models were conducted to examine the effects of chronic and episodic stress.

4. Results

Means, standard deviations and frequencies of key study variables by follow-up timepoint are presented in Table 1. We conducted a series of LMM to examine the concurrent main and interactive effects of cognitive inflexibility and chronic and episodic stress separately. For chronic stress as an indicator variable, results for Model 1 (Table 2) indicated a significant main effect for ED shift errors, but not chronic stress, on SI. There was also a significant chronic stress × ED shift errors interaction, suggesting that the relation between cognitive inflexibility and SI differed as a function of chronic stress. This finding was maintained when we statistically adjusted for the youth's demographics, including age, racial/ethnic minoritized group membership (yes, no), sex assigned at birth, and baseline depressive symptoms (Table 2).

To probe the significant interactive effect, we plotted the chronic stress × ED shift errors interaction graphically using a set of computational web tools (Bauer and Curran, 2005; Preacher et al., 2006). As Fig. 1 shows, greater ED shift errors were linked to higher SI severity, particularly among individuals with greater chronic stress. This difference emerged at levels of chronic stress that occurred above 24.1 (i.e., region of significance). Given the mean chronic stress scores for participants were approximately 22 across timepoints, these results suggest that the association between cognitive inflexibility and SI is particularly strong among youth with greater than average chronic stress and that these findings were at least partially independent from relevant participant demographic or clinical characteristics.

Table 1
Descriptive statistics for demographic characteristics and primary study variables.

Primary study variables	Mean (SD)/ N (%)
Suicidal ideation (SIQ Total Score)	
Baseline	43.22 (24.05)
6 months	23.07 (19.79)
12 months	18.73 (17.59)
18 months	19.04 (13.25)
Cognitive inflexibility (EDS errors)	
Baseline	7.41 (8.99)
6 months	4.82 (7.09)
12 months	5.19 (8.53)
Chronic stress	
Baseline	22.03 (2.78)
6 months	22.15 (2.93)
12 months	21.91 (3.30)
Episodic stress	
Baseline	14.45 (6.89)
6 months	13.83 (7.29)
12 months	11.04 (7.23)
Demographic and clinical covariates	
Age	14.97 (1.41)
Female sex assigned at birth[a]	189 (73.0 %)
Race/ethnicity[b]	
Hispanic or Latino	37 (14.3 %)
American Indian and Alaskan Native	6 (2.3 %)
Asian	14 (5.4 %)
Black or African American	27 (10.4 %)
Native Hawaiian and Other Pacific Islander	5 (1.9 %)
White	230 (88.8 %)
Depressive symptoms (CDI 2 score)	22.74 (10.19)
Unipolar depression diagnosis (current)[a]	
Major depressive disorder	189 (73.0 %)
Dysthymia	33 (12.7 %)
Depressive disorder, not otherwise specified	24 (9.3 %)

CDI 2 = Children's Depression Inventory; EDS = extra-dimensional shift; SIQ = Suicidal Ideation Questionnaire.
[a] n (% of sample).
[b] Participants were told to select all that apply.

Results of the model examining concurrent associations between episodic stress, ED shift errors, and their interactive effect showed that there was a significant main effect of episodic stress, but not ED shift errors on SI (Table 2). The episodic stress × ED shift errors interaction was nonsignificant ($p = .10$). The main effect of episodic stress was attenuated when accounting for all relevant demographic and clinical characteristics ($p = .05$).

In order to assess for prospective associations between key study variables, we conducted a series of LMM to investigate the main and interactive effect between stress, cognitive inflexibility, and chronic and episodic stress (in separate models) on SI assessed six months later. Results are presented in Table 3. No significant main or interactive effects were found.

5. Discussion

Consistent with theory and past empirical research, greater cognitive inflexibility among psychiatrically hospitalized adolescents was associated with more severe SI over the course of the year following hospital discharge, particularly for those with higher levels of chronic stress. Our results provide support for a stress-diathesis model of suicide, whereby for adolescents in the context of chronically stressful environments, an inability to flexibly shift attention in the service of generating more

Table 2
Moderating effect of stress on relationship between cognitive flexibility and suicidal ideation.

	Chronic stress				Episodic stress			
	Model 1		Model 2		Model 1		Model 2	
	(*B, SE*)	*p*	(*B, SE*)	*p*	(*B, SE*)	*p*	(*B, SE*)	*p*
Fixed effects								
Intercept	52.37 (7.69)	.00	53.92 (11.91)	.00	47.91 (2.90)	.00	44.06 (10.34)	.00
Time	−12.63 (0.80)	.00	−12.78 (0.88)	.00	-11.86 (0.83)	.00	−12.25 (0.90)	.00
Life stress	0.07 (0.34)	.85	−0.34 (0.32)	.29	0.33 (0.13)	.01	0.25 (0.13)	.05
EDS errors	-1.65 (0.65)	.01	−1.19 (0.62)	.06	-0.14 (0.17)	.41	-0.05 (0.17)	.77
Life stress x EDS errors	0.08 (0.03)	.01	0.06 (0.03)	.04	0.02 (0.01)	.10	0.01 (0.01)	.28
Age			−0.98 (0.67)	.14			-1.20 (0.66)	.07
Sex			3.66 (2.18)	.10			3.35 (2.17)	.12
Depressive symptoms			0.86 (0.97)	.00			0.84 (0.10)	.00
Minority status			−0.04 (2.41)	.99			0.13 (2.38)	.95
Random effects								
Intercept variance	151.00 (41.27)	.00	58.38 (43.69)	.18	126.36 (45.16)	.01	38.01 (48.86)	.44
Model fit								
Number of parameters	8		12		8		12	
−2 Restricted Log Likelihood	5872.95		5785.40		5839.69		5752.85	

Note: EDS errors = Number of errors made following the extra-dimensional shift on the IED task, reflecting lower cognitive flexibility.

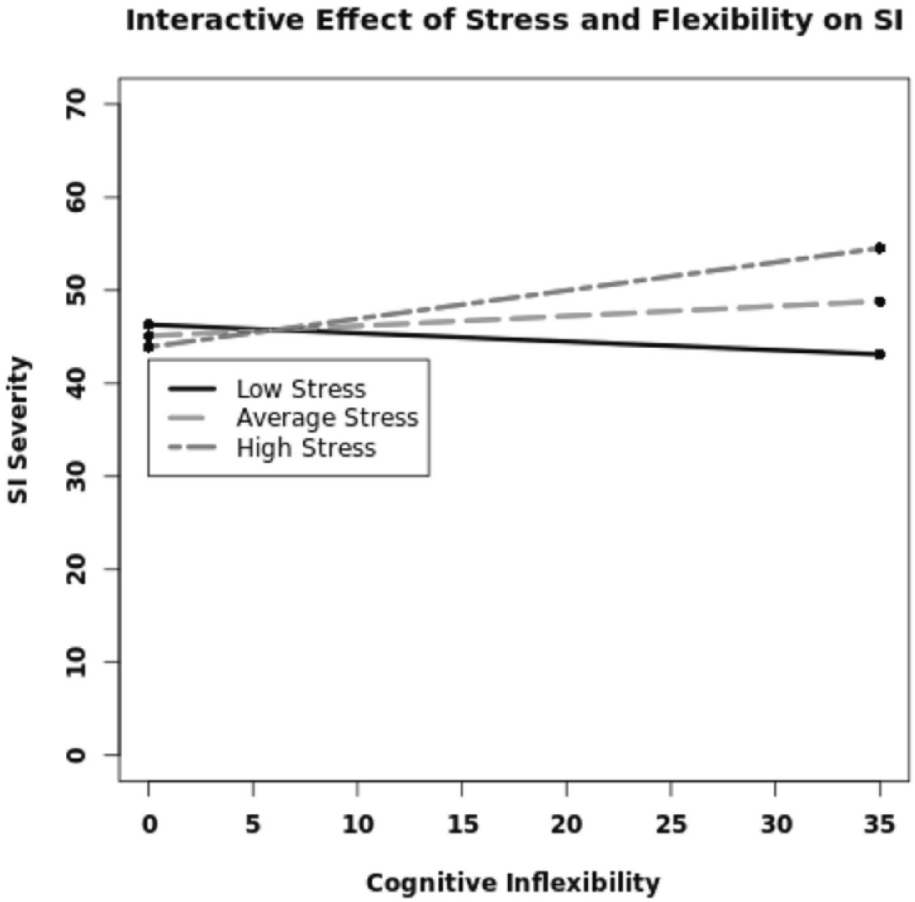

Fig. 1. The moderating effect of chronic stress on the relationship between cognitive inflexibility and suicidal ideation.

adaptive behavioral responses is associated with greater SI, at least concurrently. For adolescents without high levels of chronic stress, the effect of cognitive inflexibility on SI is attenuated. Importantly, these effects remain significant after accounting for demographic and clinical indicators of general distress, such as depressive symptoms, age, and sex, suggesting a fairly robust association with SI. This supports the assertion that cognitive flexibility may buffer the negative impact of chronic stress on SI. Cognitive inflexibility, therefore, may be a time-varying marker for vulnerability in the context of stressful environments.

In prospective analyses, however, this effect did not remain significant for chronic or episodic stress. In fact, no main effects of cognitive inflexibility or life stress were found. This result is inconsistent with

Table 3
Moderating effect of stress on relationship between cognitive inflexibility and suicidal ideation 6 months later.

	Chronic stress		Episodic stress	
	(*B, SE*)	*p*	(*B, SE*)	*p*
Fixed effects				
Intercept	23.32 (6.34)	.00	24.42 (2.41)	.00
Time	−2.18 (0.67)	.00	-2.07 (0.68)	.00
Life stress	0.11 (0.28)	.70	0.07 (0.11)	.49
EDS errors	−0.36 (0.50)	.48	-0.19 (0.14)	.17
Life stress x EDS errors	0.01 (0.02)	.66	0.00 (0.01)	.67
Random effects				
Intercept variance	60.23 (54.83)	.27	72.56 (47.03)	.12
Model fit				
Number of parameters	8		8	
−2 Restricted Log Likelihood	5084.21		5054.41	

Note: EDS errors = Number of errors made following the extra-dimensional shift on the IED task, reflecting lower cognitive flexibility.

previous findings among young adults, which found a prospective association between cognitive inflexibility and SI, even over the course of two years (Miranda et al., 2012, 2013). The current study diverges from the aforementioned study in a number of important ways that may account for these differences in findings. First, the current sample consisted of adolescents, a critical age group for prefrontal cortical development (and thus aspects of executive function, such as cognitive flexibility), whereas the former study featured an adult sample, a group for whom the prefrontal cortex should be considerably more developed. Consequently, inter-individual variability in executive function, and thus cognitive flexibility, may be more pronounced in the older sample, leading to greater potential for detecting an association with SI. Second, the current study assessed whether cognitive flexibility interacted with life stress to predict SI, whereas the prior study only assessed for a main effect between cognitive flexibility and SI.

Also worth noting is that the measure of SI in the present study assessed SI at six-month intervals. Given previous research demonstrating that SI fluctuates dramatically over the course of a month (Kleiman et al., 2017), it is possible that cognitive inflexibility under conditions of high chronic stress is predictive of SI on a shorter temporal scale than presently measured. Thus, future studies are necessary to evaluate the precise temporal parameters of this association.

Further, contrary to study hypotheses, episodic stress was not a significant moderator of the association between cognitive inflexibility and SI. This highlights the importance of utilizing contextual threat methodology when considering the effect of stress on SI among adolescents, as self-report questionnaires and checklists do not distinguish between chronic stress and episodic stress. The current study therefore builds upon prior findings by lending clarity to the stress-diathesis relationship with SI, suggesting that this association is specific to chronic, rather than episodic, stress. Events that may be considered episodic stressors for one individual may represent an aspect of an ongoing stressful context for another individual, and therefore may not be identified or assessed as discrete episodic events. The current study is one of the very few studies to examine the effect of chronic stress on SI among adolescents, with most the literature examining broad conceptualizations of stress that do not assess chronicity or context, relying heavily on reports that may conflate the two constructs. One previous study examined the interactive effect of chronic stress with a different intrapersonal vulnerability, problem solving, and SI among high-risk adolescents. Results likewise provided support for a stress-diathesis conceptual framework and highlighted the importance of using contextual threat methodology to assess the effects of both chronic and episodic stress in this developmental period (Grover et al., 2009).

The present study was the first to address several pervasive methodological limitations in previous studies. First, the use of objective neurocognitive assessment and the contextual threat interview of life stress addressed an overreliance on self-report measurement of potential vulnerability to STBs. Second, the use of a clinical sample of high-risk adolescents and consideration of clinical severity over time as a covariate more broadly allowed for a more methodologically sensitive examination of cognitive inflexibility and life stress in relation to SI specifically. In other words, cognitive inflexibility under conditions of high chronic stress may be able to further identify risk among adolescents already identified as at-risk by virtue of STB history and severe depressive symptoms. Given that the highest risk of suicidal outcomes occurs in the days to weeks after discharge from psychiatric inpatient care (Chung et al., 2017; Meehan et al., 2006; Vuagnat et al., 2019), the psychiatrically acute sample is a significant strength. The results, indeed, suggest the importance of the stress-diathesis framework in conceptualizing risk for STBs specifically among high-risk adolescents, and identifies crucial next steps for future research.

Cognitive flexibility, and executive function more generally, have largely been examined in relation to STBs as dispositional, trait-like factors (Cha et al., 2019). Yet, research has demonstrated the effect of acute stress on core executive functions, including cognitive flexibility (Shields et al., 2016). Indeed, acute stress paradigms have been shown to decrease access to remote memory representations and to bias retrieval towards close associations, suggesting that cognitive flexibility becomes impaired under stress (Harkins, 2006; Storbeck and Clore, 2008). A recent study demonstrated that cognitive inflexibility increases under social stress (Fabio et al., 2021). This suggests that acute stressors lead to state-based increases in cognitive inflexibility, making it more difficult for individuals to respond flexibly and adaptively in the moment when encountering stressful social situations. Measurement of cognitive inflexibility in moments of acute stress, particularly social stress, may more accurately reflect how this crucial executive functioning capability functions following episodic stress. However, the current study measured cognitive inflexibility in the absence of a stress induction utilizing a neurocognitive measure that contains neutral stimuli. Given the conceptualization of adolescent suicide as "a failure of biological responses to acute stress in the proximal moments of a suicidal crisis," a crucial next step would be to examine how cognitive inflexibility measured in response to an acute social stress paradigm relates to adolescent SI (Miller and Prinstein, 2019). Indeed, previous studies examining the interaction of cognitive and affective processes (e.g., negative mood or social stress induction) have been fruitful in the prospective prediction of SI and depressive symptoms (Calhoun et al., 2012; Cha et al., 2018).

6. Conclusion

In summary, the present results are the first to provide support for a cognitive inflexibility diathesis-stress model of SI in adolescents, reaffirming the importance of considering stress in understanding risk for suicide in this sensitive developmental period. This study suggests importance of future directions that understand how various cognitive risk factors create vulnerability to SI in the context of stressful environments. Many existing treatments for SI among adolescents attempt to target cognition and promote flexibility in thinking. Cognitive flexibility as a target for intervention may be most crucial for adolescents under conditions of chronic social, behavioral, or academic stress. Identification and treatment of perseverative thinking, possibly influenced by cognitive inflexibility, and identification of periods of acute and chronic stress represent important steps in reducing the proximal risk for suicidal thinking in adolescents. Future research is encouraged to affirm the directionality and time course of the effect of cognitive inflexibility as it relates to future SI under conditions of stress and investigate the temporal associations between these constructs.

Contributors

Drs. Cheek and Liu are responsible for the study design and have full access to all of the data used in the study. Dr. Cheek assumed primary responsibility for drafting the manuscript. Drs. Cheek and Kudinova are responsible for the data analyses. Ms. Kuzyk assisted with drafting the manuscript. Drs. Kudinova, Goldston, and Liu provided critical revisions for intellectual content to the final draft of the manuscript.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

Armbruster, D.J.N., Ueltzhöffer, K., Basten, U., Fiebach, C.J., 2012. Prefrontal cortical mechanisms underlying individual differences in cognitive flexibility and stability. J. Cogn. Neurosci. 24 (12), 2385–2399.

Bauer, D. J., & Curran, P. J. (2005). Probing interactions in fixed and multilevel regression: inferential and graphical techniques. *Multivariate Behavioral Research*, *40* (3), 373–400. Routledge.

Bolger, N., Laurenceau, J.P., 2013. Intensive Longitudinal Methods: An Introduction to Diary and Experience Sampling Research. Guilford Press.

Bredemeier, K., Miller, I.W., 2015. Executive function and suicidality: A systematic qualitative review. In: Clinical Psychology Review, 40, 170–183. Elsevier Ltd., Retrieved from https://doi.org/10.1016/j.cpr.2015.06.005.

Brown, Harris, 1978. Social Origins of Depression: A Study of Psychiatric Disorder in Women. Tavistock, London.

Calhoun, C.D., Franklin, J.C., Adelman, C.B., Guerry, J.D., Hastings, P.D., Nock, M.K., Prinstein, M.J., 2012. Biological and cognitive responses to an in vivo interpersonal stressor: longitudinal associations with adolescent depression. Int. J. Cogn. Ther. 5 (3), 283–299.

Cambridge Cognition, 2021. Neuropsychological Tests from Cambride Cognition. Retrieved from. https://www.cambridgecognition.com/cantab/.

Cha, C.B., O'Connor, R.C., Kirtley, O., Cleare, S., Wetherall, K., Eschle, S., Tezanos, K.M., et al., 2018. Testing mood-activated psychological markers for suicidal ideation. J. Abnorm. Psychol. 127 (5), 448–457.

Cha, C. B., Wilson, K. M., Tezanos, K. M., DiVasto, K. A., & Tolchin, G. K. (2019). Cognition and self-injurious thoughts and behaviors: A systematic review of longitudinal studies. *Clinical Psychology Review*, *69*(July 2018b), 97–111. Elsevier. Retrieved from doi:https://doi.org/10.1016/j.cpr.2018.07.002.

Chung, D.T., Ryan, C.J., Hadzi-Pavlovic, D., Singh, S.P., Stanton, C., Large, M.M., 2017. Suicide rates after discharge from psychiatric facilities: a systematic review and meta-analysis. JAMA Psychiatry 74 (7), 694–702.

Compas, B.E., 1987. Stress and life events during childhood and adolescence. Clin. Psychol. Rev. 7 (3), 275–302.

Dajani, D.R., Uddin, L.Q., 2017. Demystifying cognitive flexibility: implications for clinical and developmental neuroscience. Trends Neurosci. 38 (9), 571–578.

De Lissnyder, E., Koster, E.H.W., Goubert, L., Onraedt, T., Vanderhasselt, M.A., De Raedt, R., 2012. Cognitive control moderates the association between stress and rumination. In: Journal of Behavior Therapy and Experimental Psychiatry, 43(1), 519–525. Elsevier Ltd., Retrieved from https://doi.org/10.1016/j.jbtep.2011.07.004.

Diamond, A., 2013. Executive functions. Annu. Rev. Psychol. 64, 135–168.

Esposito-Smythers, C., Wolff, J.C., Liu, R.T., Hunt, J.I., Adams, L., Kim, K., Frazier, E.A., et al., 2019. Family-focused cognitive behavioral treatment for depressed adolescents in suicidal crisis with co-occurring risk factors: a randomized trial. J. Child Psychol. Psychiatry Allied Discip. 60 (10), 1133–1141.

Fabio, R.A., Picciotto, G., Caprì, T., 2021. The effects of psychosocial and cognitive stress on executive functions and automatic processes in healthy subjects: A pilot study. Current Psychology. Current Psychology.

Genet, J.J., Siemer, M., 2011. Flexible control in processing affective and non-affective material predicts individual differences in trait resilience. Cognit. Emot. 25 (2), 380–388.

Grover, K.E., Green, K.L., Pettit, J.W., Monteith, L.L., Garza, M.J., Venta, A., 2009. Problem solving moderates the effects of life event stress and chronic stress on suicidal behaviors in adolescence. J. Clin. Psychol. 65 (12), 1281–1290.

Hammen, C. (2005). Stress and depression. Annu. Rev. Clin. Psychol., 1(1), 293–319. Retrieved from https://doi.org/10.1146/annurev.clinpsy.1.102803.143938.

Hammen, C., 2016. Depression and stressful environments: identifying gaps in conceptualization and measurement. Anxiety Stress Coping 29 (4), 335–351.

Hammen, C., Brennan, P.A., 2001. Depressed adolescents of depressed and nondepressed mothers: tests of an interpersonal impairment hypothesis. J. Consult. Clin. Psychol. 69 (2), 284–294.

Harkins, S.G., 2006. Mere effort as the mediator of the evaluation-performance relationship. J. Pers. Soc. Psychol. 91 (3), 436–455.

Heinzel, A., Northoff, G., Boeker, H., Boesiger, P., Grimm, S., 2010. Emotional processing and executive functions in major depressive disorder: dorsal prefrontal activity correlates with performance in the intra-extra dimensional set shift. Acta Neuropsychiat. 22 (6), 269–279.

Ivey-Stephenson, A., Demissie, Z., Crosby, A.E., Stone, D.M., Gaylor, E., Wilkins, N., Lowry, R., et al., 2020. Suicidal ideation and behaviors among high school students - youth risk behavior survey, United States, 2019. MMWR supplements 69 (1), 47–55.

Kim, C., Cilles, S.E., Johnson, N.F., Gold, B.T., 2012. Domain general and domain preferential brain regions associated with different types of task switching: A meta-analysis. Human Brian Mapping 142 (33), 130–142.

Kleiman, E.M., Turner, B.J., Fedor, S., Beale, E.E., Huffman, J.C., Nock, M.K., 2017. Examination of real-time fluctuations in suicidal ideation and its risk factors: results from two ecological momentary assessment studies. J. Abnorm. Psychol. 126 (6), 726–738.

Kovacs, M., 2011. Children's Depression Inventory 2nd edition (CDI 2): Technical manual. Multi-Health Systems.

Liu, R.T., Miller, I., 2014. Life events and suicidal ideation and behavior: A systematic review. In: Clinical Psychology Review, 34(3), 181–192. Elsevier Ltd., Retrieved from https://doi.org/10.1016/j.cpr.2014.01.006.

MacPherson, H. A., Kim, K. L., Seymour, K. E., Wolff, J., Esposito-Smythers, C., Spirito, A., & Dickstein, D. P. (2022). Cognitive flexibility and impulsivity deficits in suicidal adolescents. *Research on Child and Adolescent Psychopathology*, *50*(12), 1643–1656. Springer US. Retrieved from doi:https://doi.org/10.1007/s10802-022-00952-y.

Mann, J.J., 2003. Neurobiology of suicidal behaviour. Nat. Rev. Neurosci. 4 (10), 819–828.

Mcquaid, J.R., Monroe, S.M., Mcquaid, J.R., Monroe, S.M., Roberts, J.E., Kupfer, D.J., Frank, E., 2000. A comparison of two life stress assessment approaches. Prospective Prediction of Treatment Outcome in Recurrent Depression 109 (November 2016), 787–791.

Meehan, J., Kapur, N., Hunt, I.M., Turnbull, P., Robinson, J., Bickley, H., Parsons, R., et al., 2006. Suicide in mental health in-patients and within 3 months of discharge: national clinical survey. Br. J. Psychiatry 188 (FEB.), 129–134.

Miller, A.B., Prinstein, M.J., 2019. Adolescent suicide as a failure of acute stress-response systems. Annu. Rev. Clin. Psychol. 15, 425–450.

Miranda, R., Gallagher, M., Bauchner, B., Vaysman, R., Marroquín, B., 2012. Cognitive inflexibility as a prospective predictor of suicidal ideation among young adults with a suicide attempt history. Depress. Anxiety 29 (3), 180–186.

Miranda, R., Valderrama, J., Tsypes, A., Gadol, E., & Gallagher, M. (2013). Cognitive inflexibility and suicidal ideation: mediating role of brooding and hopelessness. *Psychiatry Research*, *210*(1), 174–181. Elsevier. Retrieved from doi:https://doi.org/10.1016/j.psychres.2013.02.033.

Miron, O., Yu, K.-H., Wilf-Miron, R., Kohane, I., 2019. Suicide rates among adolescents and young adults in the United States, 2000-2017. JAMA 321 (23).

Miyake, A., Friedman, N.P., Emerson, M.J., Witzki, A.H., Howerter, A., Wager, T.D., 2000. The unity and diversity of executive functions and their contributions to complex "frontal lobe" tasks: a latent variable analysis. Cogn. Psychol. 41 (1), 49–100.

Monroe, S. M. (2008). Modern approaches to conceptualizing and measuring human life stress. Annu. Rev. Clin. Psychol., 4(1), 33–52. Retrieved from https://doi.org/10.1146/annurev.clinpsy.4.022007.141207.

Niendam, T.A., Laird, A.R., Ray, K.L., Dean, Y.M., Glahn, D.C., Carter, C.S., 2012. Meta-analytic evidence for a superordinate cognitive control network subserving diverse executive functions. Cognitive Affective Behavioral Neurosceinc 12, 241–268.

Preacher, K.J., Curran, P.J., Bauer, D.J., 2006. Computational tools for probing interactions in multiple linear regression, multilevel modeling, and latent curve analysis. In: Journal of Educational and Behavioral Statistics, 31(4), 437–448. Association, American Educational Research.

Rahmani, N., Hatch, J., Dimick, M., Naiberg, M. R., Fiksenbaum, L., Andreazza, A. C., Bowie, C. R., et al. (2021). Lower pro- to anti-inflammatory ratios associated with reduced neurocognitive flexibility in symptomatic adolescents with bipolar disorder. *Journal of Affective Disorders*, *292*(May 2019), 430–438. Elsevier B.V. Retrieved from doi:https://doi.org/10.1016/j.jad.2021.05.062.

Reynolds, W.M., 1988. Suicidal ideation questionnaire: Professional manual. Odessa: Psychol. Assess. Resour.

Reynolds, W., Mazza, J.J., 1999. Assessment of suicidal ideation in inner-city children and young adolescents: reliability and validity of the suicidal ideation questionnaire-JR. Sch. Psychol. Rev. 28 (1), 17–30.

Ribeiro, J.D., Franklin, J.C., Fox, K.R., Bentley, K.H., Kleiman, E.M., Chang, B.P., Nock, M.K., 2016. Self-injurious thoughts and behaviors as risk factors for future suicide ideation, attempts, and death: a meta-analysis of longitudinal studies. Psychol. Med. 46 (2), 225–236.

Ruch, D., Sheftall, A.H., Heck, K., McBee-Strayer, S.M., Tissue, J., Reynolds, B., Ackerman, J., et al., 2020. Neurocognitive vulnerability to youth suicidal behavior.

In: Journal of Psychiatric Research, 131(April), 119–126. Elsevier Ltd., Retrieved from https://doi.org/10.1016/j.jpsychires.2020.08.032.
Shields, G.S., Sazma, M.A., Yonelinas, A.P., 2016. The effects of acute stress on core executive functions: A meta-analysis and comparison with cortisol. In: Neuroscience and Biobehavioral Reviews, 68, 651–668. Elsevier Ltd., Retrieved from https://doi.org/10.1016/j.neubiorev.2016.06.038.
Simons, A.D., Angell, K.L., Monroe, S.M., Thase, M.E., 1993. Cognition and life stress in depression: cognitive factors and the definition, rating, and generation of negative life events. J. Abnorm. Psychol. 102 (4), 584–591.
Speckens, A.E.M., Hawton, K., 2005. Social problem solving in adolescents with suicidal behavior: a systematic review. Suicide Life Threat. Behav. 35 (4), 365–387.
Storbeck, J., Clore, G.L., 2008. The affective regulation of cognitive priming. Emotion 8 (2), 208–215.
van Heeringen, K. (2012). Stress–diathesis model of suicidal behavior. In Y. Dwivedi (Ed.), The Neurobiological Basis of Suicide (pp. 113–124). Boca Raton, FL.
Vuagnat, A., Jollant, F., Abbar, M., Hawton, K., Quantin, C., 2019. Recurrence and mortality 1 year after hospital admission for non-fatal self-harm: a nationwide population-based study. Epidemiol. Psychiatr. Sci. 29, e20.