Intolerance of uncertainty as a predictor of post-traumatic stress symptoms following a traumatic event

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1. Introduction

Exposure to a traumatic event is common among the general population, with prevalence rates of trauma exposure estimated at approximately 70–80% of individuals (Frans, Rimmiö, Åberg, & Fredrikson, 2005; Resnick, Kilpatrick, Dusky, Saunders, & Best, 1993). While responses to traumatic events vary, most individuals experience some degree of posttraumatic stress symptoms (PTSS) in the acute aftermath of a trauma (Kilpatrick and Resnick, 1993), which, when elevated, can be a risk factor for a future posttraumatic stress disorder (PTSD) diagnosis (Ullman and Filipas, 2001). Specifically, PTSS include re-experiencing the event via nightmares, flashbacks, and intrusive memories: avoidance of reminders of the event; numbing symptoms such as an inability to feel positive emotions and loss of interest in previously enjoyed activities; and hyperarousal symptoms, such as hypervigilance and trouble sleeping (Ballenger et al., 2000). A majority of individuals exposed to a traumatic event recover from these symptoms within a few months (Kilpatrick and Resnick, 1993). However, a significant minority continue to experience PTSS, with some developing clinically significant distress or impairment and meeting criteria for PTSD. Both elevated PTSS severity and PTSD are associated with a number of negative outcomes, including significant distress, interpersonal and occupational dysfunction, as well as risk for comorbid mental illnesses and suicidality (Kessler, 2000; Marshall et al., 2001).

Given the distress and impairment associated with PTSS, identifying risk factors that may contribute to increased symptomology is important. Kraemer, Lowe, and Kupfer (2005) provide a useful delineation of risk. Specifically, a true risk factor must be related to an unwanted outcome, temporally antecedent the unwanted outcome, and be malleable (Kraemer et al., 2005). Various factors have been implicated for putting an individual at risk for PTSD, such as age and gender (Brewin, Andrews, & Valentine, 2000). However, these factors cannot be changed and are considered to be fixed risk markers by Kraemer et al. (2005). Although fixed markers are important to understanding risk for PTSD, only true risk factors can be mitigated through preventative interventions.

One psychological vulnerability factor that may convey risk for increased PTSS is Intolerance of Uncertainty (IU). Individuals high in IU display a tendency to respond negatively to uncertain or ambiguous situations on a cognitive, emotional, and behav-
ioral level (Dugas, Schwartz, & Francis, 2004). In addition, they consider the possibility of a negative event occurring as unacceptable and threatening, irrespective of the probability of its occurrence (Carleton, Norton, & Asmundson, 2007). As such, individuals high in IU attempt to avoid ambiguous situations, which may lead to increased anxiety over time. Previous research has found IU to be malleable, with studies finding reductions in IU pre- to post-treatment (Boswell, Thompson-Holls, Farchione, & Barlow, 2013; Dugas and Ladouceur, 2000). Furthermore, the extant literature has shown robust associations between IU and various anxiety-related disorders, leading researchers to conceptualize IU as an important transdiagnostic individual difference variable within anxiety disorders (Carleton et al., 2012; Mahoney & McEvoy, 2012; McEvoy & Mahoney, 2012).

Despite this conceptualization, the relationship between IU and PTSD is understudied. In fact, only two studies to date have examined the relationship between IU and PTSD. For example, Fetzner, Horswill, Boelen, and Carleton (2013) investigated the relationship between IU and PTSD utilizing trauma-exposed individuals from the community. Within this sample, the authors found IU to be significantly related to the PTSD symptoms of avoidance, numbing, and hyperarousal, but not re-experiencing. In a separate study, Bardeen, Fergus, and Wu (2013) examined the relationship between IU, worry, and PTSD. Results indicated IU as a significant moderator in the relationship between worry and the hyperarousal symptom domain of PTSD within a sample of undergraduate students endorsing a traumatic life event. These findings provide initial support for a relationship between IU and increased PTSD, but a crucial gap in the literature still remains. Specifically, no research to date has examined whether IU is prospectively related to an increase in PTSD following exposure to a traumatic event. This knowledge is critical, given the importance of temporal antecedence when determining whether a variable conveys risk for a specific outcome (Kraemer et al., 2005).

Considering this gap in the literature, the current study investigated whether IU before a traumatic event would be prospectively associated with increased PTSD following a traumatic event. We hypothesized that IU before a traumatic event would predict PTSD following exposure to a trauma. Given previous research highlighting the important role of anxiety sensitivity (AS) in relation to PTSD (Bernstein et al., 2005; Naragon-Gainey, 2010; Olatunji and Wolitzky-Taylor, 2009), and more recent work demonstrating AS as a prospective predictor of PTSD following a traumatic event (Boffa et al., under review), we were also interested in looking at the relationship between pre-trauma IU and post-trauma PTSD after accounting for pre-trauma levels of AS. AS is believed to act as an amplification factor in the context of stressors (Boffa et al., under review). Therefore, we hypothesized that the relationship between pre-trauma IU and post-trauma PTSD would remain significant even after covarying for pre-trauma AS. To further examine the relationship between pre-trauma IU and PTSD following a traumatic event, we examined how IU related to the four DSM-IV PTSD symptom domains (i.e., hyperarousal, re-experiencing, numbing, and avoidance), after covarying for pre-trauma levels of AS. We hypothesized that pre-trauma levels of IU would be significantly associated with the post-trauma hyperarousal symptom domain after covarying for pre-trauma AS, given the consensus in regards to IU and this symptom cluster in previous research (Bardeen et al., 2013; Fetzner et al., 2013). No a priori hypotheses were made regarding pre-trauma IU and the remaining PTSD symptom domains (i.e., re-experiencing, numbing, and avoidance) due to limited previous research investigating these relationships.

We were also interested in an exploratory analysis focused on whether IU would interact with trauma exposure. In this sample, we found that AS interacted with level of exposure to a traumatic event to predict increased PTSD following a trauma (Boffa et al., under review). Consistent with theories of AS (Taylor, Koch, & McNally, 1992) we expected and found data consistent with the idea that high AS in the context of higher trauma exposure resulted in higher rates of PTSD. However, we considered that IU would likely be differentially related to trauma. Whereas AS amplifies responses to stress, IU is most likely to contribute to anxiety in the anticipation of a future threat versus a known or prior stressor (Carleton et al., 2012; Dugas et al., 2005; Epstein, 1972; Holaway, Heimberg, & Coles, 2006; Krohne, 1993). Accordingly, we did not hypothesize that pre-trauma IU would interact with level of exposure to a traumatic event to produce increased PTSD.

2. Methods

2.1. Participants

Participants consisted of 50 undergraduate students recruited from a large southern university. The sample was primarily female (78%), with ages ranging from 17 to 20 (M=18.22, SD=.58). The majority of the sample identified as Caucasian (82%) followed by African American (8%) and Asian (2%), with 8% declining to respond.

2.2. Procedure

Students enrolled in introductory psychology courses are required to gain exposure to research by either writing a research paper or participating in research experiments conducted within the psychology department. As a part of a screening process to determine eligibility for individual experiments, 813 students enrolled in Introductory to Psychology in fall 2014 completed a large battery of self-report questionnaires at the beginning of the semester. The entire battery took approximately one hour to complete and participants received 1 course credit for their participation. On November 21, 2014, a gunman opened fire in the campus library, leaving three students wounded before being fatally shot by police. In the weeks following this incident, students who completed the mass screening at the beginning of the fall 2014 semester were emailed a brief survey regarding their experiences with the adverse event. Eighty individuals completed this follow-up survey which took approximately 20 min to complete, with an average response time of 17.19 days (SD = 6.36) after the shooting occurred. Of the 80 individuals who completed the follow-up assessment, 25 reported no direct exposure (i.e., did not directly experience, witness, or learn about the event occurring to someone they were close to) and thus were excluded from the current analyses. In addition, data were missing from another 5 individuals bringing the final sample size to 50. As compensation for participation, all individuals who completed the follow-up assessment were entered into a drawing for the chance to win one of three $50 Visa gift cards. All procedures for the study were approved by the university’s Institutional Review Board and informed consent was obtained prior to data collection.

2.3. Measures

2.3.1. Anxiety sensitivity index (ASI)

The ASI is a 16-item self-report questionnaire measuring the feared physical, cognitive, and social consequences associated with anxious arousal (Reiss, Peterson, Gursky, & McNally, 1986). Participants were asked to rate how much they agreed with each item on a 5-point Likert-type scale ranging from 0 (very little) to 4 (very much). The ASI has previously demonstrated good psychometric properties (Taylor et al., 1992). The ASI was administered initially at screening and during the follow-up assessment. In the
present investigation only the screening total score was included as a covariate. Internal consistency was good at screening ($\alpha = .89$).

2.3.2. Intolerance of uncertainty scale (IUS)

The IUS is a 27-item self-report questionnaire assessing the degree to which individuals are able to tolerate uncertainty of ambiguous situations, the cognitive and behavioral responses to uncertainty, perceived implications of uncertainty, and attempts to control the future (Freeston, Rhéaume, Letarte, Dugas, & Ladouceur, 1994). Items are rated on a 5-point Likert-type scale ranging from 0 (Not at all characteristic of me) to 5 ( Entirely characteristic of me). Due to space constraints in the mass screening, only three items of the IUS-27 were administered in the initial screening battery (item 5 “My mind can’t be relaxed if I don’t know what will happen tomorrow,” item 6 “Uncertainty makes me uneasy, anxious, or stressed,” and item 26 “The ambiguities in life stress me out”), however, correlation analyses found our abbreviated index of IUS to be highly associated with the IUS-27 total score in various clinical, undergraduate, and community samples (r’s range from .87 to .90). Therefore, we believe that our abbreviated IUS total score is representative of the overall construct of IU and permissible to use. The IUS has demonstrated good psychometric properties including high internal consistency, retest reliability, and convergent and divergent validity (Buhr and Dugas, 2002). In the current sample, the three IUS items (IUS-3) demonstrated excellent internal consistency ($\alpha = .91$).

2.3.3. Physical exposure questionnaire (PEQ)

The PEQ is a 15-item self-report questionnaire designed to assess level of exposure to the shooting as it occurred. This measure was adapted from previous research examining trauma exposure (Littleton, Grills-Taquechel, & Assom, 2009; Stephenson, Valentiner, Kumpula, & Orcutt, 2009). Specifically, participants were asked to respond “Yes” or “No” to various questions designed to determine ones proximity to the event. Furthermore, responses to specific questions are summed to create a “moderate” and “high” exposure level score. From this measure, participants were selected if they endorsed moderate or high exposure to the shooting. Of the final sample, 50% (n = 25) individuals reported being in a campus building that was locked-down, or saw police surround the building, but did not report any other experiences, and were categorized as ‘moderate’ exposure. The other 50% (n = 25) of the sample endorsed experiencing ‘high’ exposure to the shooting, such as being in the building where the shooting occurred, hearing gunfire, seeing the gunman or the gunman fire upon anyone, seeing individuals wounded, or knowing someone who was wounded.

2.3.4. Posttraumatic stress disorder checklist (PCL-C)

The PCL-C is a 17-item self-report measure assessing various symptoms of PTSD (Weathers, Litz, Herman, Huska, & Keane, 1994). In the current study, the PCL-C was administered only at follow-up and was modified to specifically index symptoms related to the recent campus shooting. In particular, participants were asked to indicate the degree to which they had been bothered by each problem on a 5-point Likert-type scale ranging from 1 (Not at all) to 5 (Extremely) since the shooting occurred, and as a direct result of their experience with the shooting with the following prompt: “The following questions will now focus on your direct experience with the shooting that occurred at Strozier Library on the FSU campus in November. Please answer all questions as they relate to your experiences since that time.” In addition to a total score, the PCL-C yields four subscales including hyperarousal, re-experiencing, numbing, and avoidance. The PCL-C has demonstrated good psychometric properties in prior research (Wilkins, Lang, & Norman, 2011). Likewise, the PCL-C total score and subscale scores demonstrated good excellent internal consistency within the present investigation ($\alpha$’s ranged from .82 to .95).

### Table 1

Zero-order correlation, means, and standard deviations.

<table>
<thead>
<tr>
<th>Measure</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>M (SD)</th>
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<tbody>
<tr>
<td>1. ASI</td>
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<td>1.00</td>
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<td>2. IUS-3</td>
<td>.61</td>
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<td></td>
<td>.60 (2.41)</td>
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<tr>
<td>3. PCL total</td>
<td>.50</td>
<td>.51</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.79 (2.94)</td>
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<tr>
<td>4. PCL re-exp</td>
<td>.49</td>
<td>.51</td>
<td>.94</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.81 (3.76)</td>
</tr>
<tr>
<td>5. PCL hyper</td>
<td>.42</td>
<td>.50</td>
<td>.93</td>
<td>.82</td>
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<td>.90 (4.90)</td>
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<td>6. PCL avoid</td>
<td>.40</td>
<td>.39</td>
<td>.80</td>
<td>.74</td>
<td>.62</td>
<td></td>
<td></td>
<td>.34 (1.94)</td>
</tr>
<tr>
<td>7. PCL numb</td>
<td>.50</td>
<td>.42</td>
<td>.94</td>
<td>.87</td>
<td>.83</td>
<td>.73</td>
<td></td>
<td>.70 (3.44)</td>
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</table>

*Note. ASI = anxiety sensitivity index; IUS-3 = intolerance of uncertainty scale; 3-item total score (items 5, 6, 28); PCL-C = post-traumatic checklist, civilian version; PCL re-exp = re-experiencing symptoms; PCL hyper = PCL-C hyperarousal symptoms; PCL avoid = PCL-C avoidance symptoms; PCL numb = PCL-C numbing symptoms.*

#### 3. Results

3.1. Preliminary analyses

The means, standard deviations, and zero-order correlations for all variables of interest in the current sample are described in Table 1. As hypothesized, total post-trauma PCL-C scores were significantly correlated with pre-trauma IUS-3 scores. In addition, post-trauma PCL-C scores were significantly associated with pre-trauma ASI scores. The IUS-3 and ASI were both significantly correlated with each of the four PCL-C symptom clusters (i.e., hyperarousal, re-experiencing, avoidance, and numbing). Finally, pre-trauma ASI and IUS-3 scores were also significantly correlated with one another.

3.2. Primary analyses

To test our primary hypothesis, a linear regression analysis was conducted to assess the relationship between pre-trauma IU and post-trauma PTSS after covarying for pre-trauma AS (i.e., ASI total score). Pre-trauma AS and pre-trauma IU scores were entered into Step 1 of the model. The overall model was significant [$F (2, 47) = 10.64, p < .001$, $r^2 = .312$]. Consistent with hypotheses, pre-trauma IU [$\beta = .32$, $t = 2.12$, $p = .04$, $r^2 = .07$] significantly predicted post-trauma PTSS above and beyond pre-trauma AS [$\beta = .30$, $t = 1.95$, $p = .06$, $r^2 = .06$], which was only marginally significant in relation to post-trauma PTSS.

Next, a series of linear regression analyses were conducted to assess the relationships between pre-trauma IU and each of the four post-trauma PTSS clusters (i.e., hyperarousal, re-experiencing, emotional numbing, and avoidance) after covarying for pre-trauma AS. Pre-trauma AS and pre-trauma IU scores were entered into Step 1 of the models. In each of these analyses, the overall model was significant (all $p’s < .01$). As hypothesized, pre-trauma IU was significantly related to the hyperarousal PTSS cluster [$\beta = .38$, $t = 2.41$, $p = .02$, $r^2 = .09$]; however, pre-trauma AS was not significantly related to the hyperarousal PTSS cluster [$\beta = .19$, $t = 1.23$, $p = .23$, $r^2 = .02$]. Though not originally hypothesized, pre-trauma IU was significantly related to the re-experiencing PTSS cluster [$\beta = .33$, $t = 2.17$, $p = .04$, $r^2 = .07$], but pre-trauma AS was only marginally significant in relation to the re-experiencing PTSS cluster [$\beta = .29$, $t = 1.90$, $p = .06$, $r^2 = .05$]. Pre-trauma IU was not significantly related to the avoidance PTSS cluster [$\beta = .23$, $t = 1.38$, $p = .17$, $r^2 = .03$], nor was pre-trauma AS [$\beta = .26$, $t = 1.54$, $p = .13$, $r^2 = .04$]. Pre-trauma IU was not significantly related to the emotional numbing PTSS cluster [$\beta = .19$, $t = 1.17$, $p = .25$, $r^2 = .02$].
However, pre-trauma AS was significantly related to the emotional numbing PTSS cluster [$\beta = .38$, $t = 2.43$, $p = .02$, $s_r^2 = .09$].

We also evaluated whether pre-trauma IU and level of trauma exposure would interact to produce elevated post-event PTSS. Level of exposure (moderate vs high; as measured by the PEQ), the centered predictor variable of pre-trauma IU, and the centered interaction term of level of exposure by pre-trauma IU were entered into Step 1 of a linear regression analysis with post-trauma PTSS as the dependent outcome variable. Consistent with expectation, the interaction between level of trauma exposure and pre-trauma IU did not significantly predict post-trauma PTSS [$\beta = .62$, $t = 1.43$, $p = .16$, $s_r^2 = .03$].

4. Discussion

Consistent with initial prediction, pre-trauma levels of IU were significantly associated with elevated PTSS following exposure to a traumatic event. These results were significant even after covarying for AS, a well-established risk factor for increased PTSS. Our findings are consistent with previous research suggesting that IU plays an important role in the development of PTSS (Bardeen et al., 2013; Fetzer et al., 2013). Furthermore, our results corroborate IU as an important transdiagnostic individual difference variable for various anxiety-related disorders (Carleton et al., 2012; Mahoney and McEvoy, 2012). Our findings are particularly novel for two reasons. First, the current study is the first to investigate whether IU predicts PTSS following a trauma within a longitudinal framework. Furthermore, our results found a prospective association between pre-trauma IU and post-trauma PTSS above and beyond the relationship between pre-trauma AS. Given previous research suggesting the important role of AS in the development and maintenance of PTSS (Bomyea, Rishbourgh, & Lang, 2012; Elwood, Hahn, Olatunji, & Williams, 2009), our findings provide an important addition to the literature by identifying a potentially more important risk factor for increased PTSS.

As hypothesized, results also indicated that pre-trauma levels of IU were significantly related to the post-trauma hyperarousal symptom domain after covarying for pre-trauma levels of AS. These findings are in line with prior research finding IU to be significantly associated with the hyperarousal PTSD symptom domain (Fetzer et al., 2013). In addition, this finding is consistent with Bardeen et al. (2013) in which IU was found to significantly moderate the relationship between worry and the PTSS hyperarousal cluster. Taken together with previous work, our findings suggest that for individuals high in IU hyperarousal may play a particularly important role following a trauma. Specifically, individuals with elevated IU may be hypervigilant in order to reduce future danger by eliminating uncertainty (Bardeen et al., 2013). In addition, these individuals may fear the uncertainty regarding the reoccurrence of such a trauma, resulting in increased hyperarousal symptoms (e.g., jumpy, on guard; Fetzer et al., 2013). This finding is crucial, given previous research finding poor outcomes in relation to the hyperarousal symptom domain. Specifically, previous work has suggested that for individuals with PTSS, hyperarousal symptoms are associated with increased symptomology, reduced recovery, and the development of clinically significant symptoms following a traumatic event (Bardeen et al., 2013; Marshall, Schell, Glynn, & Shetty, 2006; Schell, Marshall, & Jaycox, 2004).

Unexpectedly, we found a significant association between pre-trauma IU and post-trauma symptoms of re-experiencing above and beyond pre-trauma levels of AS. Although Fetzer et al. (2013) did not find a significant association between IU and PTSD re-experiencing symptoms after accounting for the other symptom clusters (i.e., hyperarousal, emotional numbing, and avoidance), the authors did note a significant correlation between IU and re-experiencing symptoms with results demonstrating a trend towards significance in a regression analysis. Given that the current study and Fetzer et al. (2013) utilized non-clinical samples, time since the experience of the traumatic event may explain our somewhat disparate findings. Specifically, in the Fetzer et al. (2013) sample, participants reported experiencing a traumatic event 1–53 months prior to data collection. However, data collection in our sample was much closer to the experience of the trauma, with participant response approximately 18 days after the event. Therefore, we would expect a larger amount of fearful intrusive images (i.e., re-experiencing) directly following the traumatic event versus years after the experience of a trauma, particularly for non-clinical individuals.

The literature suggests that level of exposure may play an important role in the relationship between AS and PTSS. Within our same sample, Boffa et al. (2015) found the interaction between pre-trauma levels of AS and level of exposure to the traumatic event to predict increased post-trauma PTSS. These findings are consistent with previous research suggesting that physiological arousal during exposure to a traumatic film moderates the relationship between AS and elevated PTSS following film exposure (Olatunji and Fan, 2015). However, we did not expect similar interactive effects in terms of IU. Whereas exposure level is likely to yield greater stress responses that are relevant to the amplification effects of AS, in the case of IU, individuals primarily fear the repercussions associated with future uncertainty, regardless of the intensity of stressful events that have occurred. Consistent with this, we did not find a significant interaction between level of trauma exposure and pre-trauma IU when predicting post-trauma PTSS.

Taken together, the results of the current study are promising when considered in light of treatment implications. The extant literature supports the notion of IU as a central transdiagnostic individual difference variable in the development and maintenance of various anxiety-related and mood disorders, including symptoms of PTSD (Carleton et al., 2012; Fetzer et al., 2013; McEvoy and Mahoney, 2012). Given that previous research has shown IU to be malleable and amenable to treatment (Bowdwell et al., 2013; Ladouceur, Gosselin, & Dugas, 2000), developing prevention and intervention protocols aimed at reducing IU would be important. Furthermore, the results of this study suggest that IU may be a valuable focus of treatment for individuals at risk for developing PTSD given the shortcomings often associated with traditional PTSD treatment. Specifically, PTSD treatment is often associated with high dropout rates and many individuals remain symptomatic following treatment (Hendriks, De Kleine, & Van Minnen, 2015; Schnurr et al., 2015; Schnurr et al., 2007). In addition, existing prevention and intervention protocols for individuals with PTSD may benefit from the inclusion of techniques aimed at reducing IU (e.g., behavioral exposure to uncertain scenarios). Future work should develop and test the effectiveness of IU-specific treatments in regards to individuals with PTSD elevating PTSS.

Limitations of the current study should be considered in light of future work. Although scores from the full IUS were unavailable prior to the shooting, our abbreviated measure of IU correlated highly with the full scale in three independent samples. Furthermore, the abbreviated measure did not allow us to assess for differential relationships between the prospective and inhibitory IU subscales and PTSS. Due to the unpredictable nature of our data we do not have information regarding PTSS levels prior to the event, and therefore cannot account for baseline PTSS symptoms in the current analyses. Furthermore, diagnostic information was not collected, thus we can only look at post-trauma symptom level data as an outcome variable. Future work should aim to replicate these findings within a clinical sample while covarying for baseline PTSS. On average, PTSS (PCL-C mean) were lower than the suggested clinical cut-off (Weathers and Ford, 1996), however several indi-
viduals in the current sample reported symptom levels that have demonstrated stability from one-week to 12-months post-trauma in prior studies, resulting in a likely PTSD diagnosis (O’Donnell, Elliott, Lau, & Creamer, 2007). Lastly, given the relatively small sample at follow-up, it is possible that these results may not be representative of the overall population. Future investigations should attempt to replicate these results in larger samples.

Despite these limitations, the current study provides valuable information regarding the relationship between IU and PTSS. As previously noted, this investigation is the first to find IU as a prospective predictor of increased PTSS following a traumatic event. Although previous research has found associations between IU and symptoms of PTSD, no research to date has looked at this relationship within a longitudinal framework. Given the significant negative outcomes associated with elevated PTSS and PTSD, our findings provide a crucial addition to the literature by highlighting an important individual difference factor that may be contributing to increased symptoms. Given the malleable nature of IU (Bowell et al., 2013; Ladouceur et al., 2000), the creation and utilization of IU-specific treatments aimed at reducing symptoms of PTSD could be beneficial. Future work investigating the relations between IU and elevated PTSS within clinical samples and the effectiveness of IU-based protocols is critical for these findings to generalize.

Conflict of interest

The authors of this manuscript do not have any actual or potential conflicts of interest to report or disclose.

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Contributors

Author one wrote the majority of the introduction and discussion sections, as well as assisted with the methods and results sections. Author two assisted with writing the results section as well as assisting with the introduction and discussion sections. Author three wrote the methods section and conducted literature searches. Author four assisted with the introduction and discussion sections as well as proof reading and writing assistance. Author five provided critical feedback on all drafts of the manuscript. All authors contributed significantly to the manuscript and approved the final version being submitted.

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