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Responding to uncertain threat: A potential mediator for the effect of mindfulness on anxiety

Inka Papenfuss [a,*], Miriam J.J. Lommen [a], Christian Grillon [b], Nicholas L. Balderston [b,c], Brian D. Ostafin [a]

[a] Department of Clinical Psychology and Experimental Psychopathology, University of Groningen, Groningen, Netherlands
[b] Section on the Neurobiology of Fear and Anxiety, National Institute of Mental Health, Bethesda, MD, United States
[c] Center for Neuromodulation in Depression and Stress, Department of Psychiatry, University of Pennsylvania, PA, United States

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ABSTRACT

Mindfulness-based interventions have gained extensive support for their application in the treatment of anxiety. However, their mechanisms remain largely unexplored. Excessive reactivity to uncertainty plays a central role in anxiety, and may represent a mechanism for the effect of mindfulness on anxiety, as mindfulness training fosters an open and accepting stance towards all aspects of experience. The present study sought to investigate both (i) self-reported intolerance of uncertainty (IU) as well as (ii) physiological and subjective responding to uncertain threat in a threat-of-shock paradigm, the NPU-threat test, as mediators for the relationship between mindfulness and anxiety in a cross-sectional study of healthy participants ($N = 53$). The results indicated that IU mediated the effect of mindfulness on some anxiety symptoms. In contrast, scores of physiological as well as subjective responses to uncertain threat from the NPU-threat test were largely unrelated to mindfulness, anxiety, or the IU self-report measure. The results provide initial evidence that reactions to uncertainty may play a role in the mindfulness-anxiety relationship and suggest that studies are needed to address how methodological variations of the NPU-threat test affect perceived levels of uncertainty and uncertainty-related anxiety.

1. Introduction

With lifetime prevalence estimates of 28.8 %, anxiety disorders are the most common class of mental disorders (Kessler et al., 2005), and they are associated with substantial functional impairment and reduced quality of life (Lochner et al., 2003). Although first-line interventions such as CBT are effective (e.g., Hofmann, Asnaani, Vonk, Sawyer, & Fang, 2012), up to 21 % of patients do not complete treatment, and about 35 % do not benefit sufficiently (Taylor, Abramowitz, & McKay, 2012). Among those who do improve, relapse occurs in over 50 % of cases within two years (Westen & Morrison, 2001). Hence, there is considerable room for improvement, which underscores the need for developing new treatments and modifying existing treatment approaches.

Mindfulness-based interventions constitute one promising class of approaches for the treatment of anxiety. Mindfulness meditation has its origins in Buddhism, where it has long been believed to represent one element of a way of eliminating suffering (Teasdale & Chaskalson, 2011). Mindfulness interventions for psychological distress have relatively recently found their way to the West and have spurred research programs into its benefits. The practice of mindfulness is commonly defined as being aware of and paying attention to one's subjective experience in the present moment and exhibiting an accepting attitude towards that experience (Kabat-Zinn, 2015). Approaches to therapy such as mindfulness-based cognitive therapy combine mindfulness meditation with techniques used in conventional therapy to promote well-being (Bishop, 2004). Evidence in support of its usefulness comes from research showing inverse associations between mindfulness and anxiety (e.g., Baer, Smith, Hopkins, Krietemeyer, & Toney, 2006; Ostafin, Brooks, & Laitem, 2014) and from experimental studies (e.g., Arch et al., 2013), and meta-analyses (Hofmann, Sawyer, Witt, & Oh, 2010) on the effectiveness of mindfulness-based interventions in the treatment of anxiety.

Although evidence for the benefits of mindfulness is accumulating, the mechanisms through which it affects anxiety are as yet barely explored. It is an important avenue for research to elucidate these

* Corresponding author.
E-mail address: i.papenfuss@rug.nl (I. Papenfuss).

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mechanisms, as such findings can inform the development and optimization of treatment. One potential mechanism concerns reactivity towards uncertainty. Individual differences in the sensitivity to uncertainty have repeatedly been shown to play a role across anxiety disorders. We argue that the accepting stance associated with mindful awareness promotes tolerance towards uncertain aspects of experience, thereby reducing the likelihood of dysfunctional uncertainty-related responses that may contribute to anxiety. The aim of the present study is to investigate the proposal that reactivity to uncertainty mediates the inverse relationship between mindfulness and anxiety.

2. Uncertainty – the stressor of not knowing

Uncertainty has long been implicated in models of anxiety. Anxiety has been defined as encompassing emotional, cognitive, and behavioural responses in anticipation of uncertain threat (Grupe & Nitschke, 2013), and it is thought to serve the purpose of preparing for the potential occurrence of this threat (Barlow, 2002). Thus, uncertainty is thought to be central to the experience of anxiety, and it has been argued that extreme responses to uncertainty play a critical role in pathological anxiety (Grupe & Nitschke, 2013).

Dysfunctional responses to uncertainty have been described as the construct of intolerance of uncertainty (IU). IU is defined as a disposition rooted in negative beliefs about uncertainty that is reflected in adverse cognitive and emotional reactions in anticipation of (i.e., *prospective IU*), as well as behavioral inhibition in response to (i.e., *inhibitory IU*), uncertainty (Dugas & Robichaud, 2007; McEvoy & Mahoney, 2011). Research using self-report measures of IU has shown that individuals high in IU are prone to perceiving ambiguous situations as threatening (e.g., interpreting a headache as a sign of a brain tumor; Dugas et al., 2005) and tend to overestimate the probability and impending costs of the occurrence of an uncertain threat (e.g., thinking that appearing unintelligent is a likely outcome of giving a presentation; Bredemeier & Berenbaum, 2008). As a result, such individuals may engage in maladaptive behaviours such as cognitive and behavioural avoidance that serve the goal of reducing uncertainty (Norr et al., 2013). Instances of this can readily be observed in anxiety disorders. For instance, worry in generalized anxiety or obsessions and compulsions in obsessive-compulsive disorder diminish perceived uncertainty and foster a sense of control (Fergus & Wu, 2010). In the short term these behaviours indeed reduce uncertainty and related anxiety, but maintain the uncertainty and anxiety in the long run.

Consequently, IU is thought to be a transdiagnostic vulnerability factor for anxiety psychopathology. Research corroborates this idea, as individual differences in IU have been related to symptoms of anxiety disorders in non-clinical (Norr et al., 2013) and clinical samples (McEvoy & Mahoney, 2011), even when controlling for other vulnerability factors such as neuroticism (McEvoy & Mahoney, 2011), anxiety sensitivity (Boelen & Reijntjes, 2009), and negative affect (Norr et al., 2013). Moreover, a recent meta-analysis showed that, with the exception of larger associations with symptoms of generalized anxiety disorder, associations with IU are largely comparable across anxiety disorders including social anxiety disorder, panic disorder, agoraphobia, and obsessive-compulsive disorder, substantiating it's transdiagnostic importance (McEvoy, Hyett, Shihata, Price, & Strachan, 2019). IU has also been shown to predict occurrence of anxiety in interaction with life stressors, substantiating its role as a factor in the development of anxiety disorders (Chen & Hong, 2010). Furthermore, treatment for anxiety disorders using a transdiagnostic intervention led to a reduction in IU that was associated with decrease in symptoms, suggesting that IU may be a change factor across diagnoses (Boswell, Thompson-Hollands, Farchione, & Barlow, 2013). Thus, the role of response to uncertainty as measured with self-report IU has been established as a factor across anxiety pathology. However, self-report scales can be subject to biases such as limited introspective abilities or unclear understanding of concepts (Demetriou, Ozer, & Essau, 2014), which is particularly relevant when probing responses to abstract concepts such as uncertainty.

Another way of measuring reaction to uncertainty involves experimentally manipulating the uncertainty associated with a threat (e.g., electrical stimulus) in the laboratory. This is typically done by varying the temporal predictability or another property related to predictability (e.g., intensity, reinforcement rate) of a threat in threat-of-shock paradigms and assessing self-reported anxiety as well as physiological indicators of aversive emotional states such as startle reflex or skin conductance. Here, unpredictable aversive stimuli evoke prolonged aversive states that are typical of sustained anxiety rather than transient fear responses (Grillon, Baas, Lissek, Smith, & Milstein, 2004). This manifests in heightened physiological reactions such as startle (Grillon et al., 2004) as well as subjective reactions such as self-reported anxiety (e.g., Shankman, Robison-Andrew, Nelson, Altman, & Campbell, 2011) during the absence of threat cues in the context of unpredictable, relative to predictable, threat. This is thought to occur because predictable threat allows for predictable periods of safety when cues signalling threat are absent. In contrast, when threat is unpredictable, safety is also unpredictable, which is thought to lead to the prolonged state of anxious anticipation in unpredictable contexts (Seligman & Binik, 1977). This context-potentiated reactivity makes it a potentially useful paradigm for studying individual differences in response to uncertainty in the laboratory.

Studies using paradigms of this kind have shown that anxiety vulnerable individuals (e.g., high in behavioural inhibition; Allen, Myers, & Servatius, 2016) as well as individuals with anxiety disorders (e.g., panic disorder, social anxiety disorder, PTSD; Gorka, Lieberman, Klumpp et al., 2017; Grillon et al., 2008, 2009) exhibit enhanced startle in response to unpredictably timed aversive stimuli. Furthermore, IU has been found to predict increased startle when an aversive shock was less predictable (Chin, Nelson, Jackson, & Hajcak, 2016). These findings provide additional evidence that individuals vulnerable to experiencing anxiety exhibit higher reactivity in the context of uncertain threat.

3. Mindfulness – accepting the unknown

Given that the acceptance element of mindfulness essentially involves giving up the goal of changing one's experience and instead allowing experience to be as it is, mindfulness-based approaches have been suggested to be particularly helpful in the treatment of disorders that are characterized by intolerance of negative experience (Bishop, 2004). With regard to anxiety, mindful acceptance may thus help to regulate aversive reactions to uncertainty, in that uncertainty should be less likely to be perceived as something that is unacceptable or that needs to be stopped. Thus, we propose that reactivity to uncertainty may represent one mechanism through which mindfulness regulates anxiety. Initial cross-sectional research supports this idea, as self-reported IU has been found to mediate the relationship between mindfulness and health anxiety (Kraemer, O'Bryan, & McLeish, 2016).

The current study was designed to extend the Kraemer et al. findings by examining whether the mediation also holds for other types of anxiety symptoms and holds when using an indirect measure of uncertainty response (i.e., threat-of-shock paradigm). We used disorder-specific anxiety measures in order to assess the transdiagnostic relevance of mindfulness and its potential mechanisms. We hypothesize (1) that mindfulness will be inversely related to symptoms of anxiety, (2a) that mindfulness will be inversely associated with self-reported IU, (2b) that IU will be associated with symptoms of anxiety, and (2c) that IU will statistically mediate the relationship between mindfulness and anxiety. With a threat-of-shock paradigm, we further hypothesize that (3a) mindfulness will be inversely associated with startle responses as well as subjective anxiety ratings in the context of unpredictable threat, (3b) these context-potentiated responses will be associated with symptoms of anxiety, and (3c) the context-potentiated responses will mediate the relationship between mindfulness and symptoms of anxiety.

4. Method

4.1. Participants

Fifty-five participants (32 female, $M_{age} = 23.25$, $SD_{age} = 3.87$) were recruited through the first-year participants pool or the paid participants pool of the University of Groningen. The former ($n = 7$) participated for fulfilment of program requirements while the latter ($n = 48$) received financial compensation.

For analyses that included startle magnitude and subjective anxiety ratings assessed in the threat-of-shock test, participants were excluded if they did not complete the task ($n = 2$) or pay attention to the task ($n = 1$), in case of technical issues ($n = 2$), or if they were classified as non-responders (i.e., there were < 2 valid startle responses per condition and cue presence [N_{Cue}, N_{ITI}, P_{Cue}, P_{ITI}, U_{Cue}, U_{ITI}] (see below); $n = 2$). The final sample used in these analyses consisted of 48 participants (28 female, $M_{age} = 23.04$, $SD_{age} = 3.91$).

The study was approved by the ethical committee of the department of psychology at the University of Groningen.

4.2. Questionnaires[1]

4.2.1. Panic and social anxiety symptoms

Symptoms of social anxiety (10 items; e.g., "giving a speech"), interoceptive fear (5 items; e.g., "playing a vigorous sport on a hot day"), and agoraphobia (9 items; e.g., "going through a car wash") were assessed with the Albany Panic and Phobia questionnaire (APPQ; Rapee, Craske, & Barlow, 1994). Items describe situations that typically induce fear in affected individuals. Participants rate the items on a scale ranging from 0 (*no fear*) to 8 (*extreme fear*), according to how much fear the participant anticipates experiencing in case of an encounter during the following week. Internal consistency for social anxiety was good ($\alpha = .89$), while that for interoceptive fear ($\alpha = .76$) and agoraphobia ($\alpha = .77$) was acceptable.

4.2.2. Worry

Worry was assessed using the Penn State Worry Questionnaire (PSWQ; Meyer, Miller, Metzger, & Borkovec, 1990). The questionnaire consists of 16 self-statements concerning experiences related to worrying (e.g., "I'm always worrying about something"), which participants rate according to how much the statements are true for them on a scale ranging from 1 (*does NOT describe me*) to 5 (*describes me PERFECTLY*). Internal consistency was excellent ($\alpha = .93$).

4.2.3. Obsessive compulsive symptoms

Symptoms of obsessive-compulsive disorder were assessed using the Obsessive Compulsive Inventory – Revised (OCI-R; Foa, Huppert, Leiberg, Hajcak, & Langner, 2002). It consists of 18 self-statements describing symptom behaviours (e.g., "I check things more often than necessary") that are rated on a scale ranging from 0 (*not at all*) to 4 (*extremely*) according to how much these behaviours have distressed the participant over the past month. Internal consistency was good ($\alpha = .84$).

4.2.4. Mindfulness

Trait mindfulness was assessed using the Five Facet Mindfulness Questionnaire – short form (FFMQ-sf; Bohlmeijer, ten Klooster, Fledderus, Veehof, & Baer, 2011). It consists of 24 self-statements that measure five factors thought to represent mindfulness: nonreactivity (5 items; e.g., "Usually when I have distressing thoughts or images, I can just notice them without reacting"), observing (4 items; e.g., "I notice the smells and aromas of things"), acting with awareness (5 items; e.g., "I find it difficult to stay focused on what's happening in the present moment"; reverse-scored), describing (5 items; e.g., "I'm good at finding the words to describe my feelings"), and non-judging (5 items; e.g., "I tell myself that I shouldn't be feeling the way I'm feeling"; reverse-scored). Items are rated on a scale ranging from 1 (*never or very rarely true*) to 5 (*very often or always true*) according to how frequently the participant has made that experience over the past month. The full score was used to reduce the number of analyses (e.g., Vøllestad, Sivertsen, & Nielsen, 2011). The FFMQ-SF showed good internal consistency ($\alpha = .86$).

4.2.5. Intolerance of uncertainty

Intolerance of uncertainty (IU) was assessed with the Intolerance of Uncertainty Scale-short form (IUS-12; Carleton, Norton, & Asmundson, 2007). It consists of 12 self-statements describing responses to uncertainty which measure two factors thought to represent the construct: prospective IU (7 items; cognitive/emotional facet; e.g., "Unforeseen events upset me greatly") and inhibitory IU (5 items; behavioural facet; e.g., "When it's time to act, uncertainty paralyzes me"). Items are rated on a scale ranging from 1 (*not at all characteristic of me*) to 5 (*entirely characteristic of me*). Although there is some evidence to suggest that the relative importance of the subscales may differ between types of anxiety, studies have generally shown that both subscales are important across the anxiety disorders (Carleton et al., 2012; McEvoy & Mahoney, 2011). Thus the full score was used to test the main hypotheses. Internal consistency of the overall scale showed excellent internal consistency ($\alpha = .91$), as did the inhibitory ($\alpha = .84$), and prospective ($\alpha = .90$) subscales.

4.3. Threat-of-shock: NPU-threat test

The threat-of-shock task (NPU-threat test) was adapted from Grillon et al. (2004) and administered with E-Prime 2.0 software (Psychology Software Tools Inc.). The task was preceded by a startle habituation phase, during which an acoustic startle probe was delivered binaurally nine times to reduce initial startle reactivity, with intervals between probes ranging from 10 to 21 s. An individual shock workup procedure was conducted to determine a shock level that was "highly annoying but not painful". Following this, the NPU-threat test was administered. The test consists of multiple presentations of three within-subjects conditions, one in which no shock was delivered (N), a predictable shock condition (P), and an unpredictable shock condition (U). Each condition lasted 2 min and during this time a geometric cue was presented 3 times for 8 s. In the N condition, the cue was a green circle that had no signal value, as no shock was delivered in this condition. In the P condition, the cue was a red square and was only delivered in the presence of the cue, 959 ms before cue offset (one shock of 100 ms duration was delivered during each P condition). In the U condition, the cue was a blue triangle and had no signal value as the shock was delivered in the intervals between cues (one shock of 100 ms duration was delivered during 50 % of the U conditions over the course of the test, and two shocks were delivered during the other 50 %). In addition, written statements with information concerning the shock contingencies (i.e., "no shock", "shock only during red square", and "shock at any time") were presented on the monitor for the whole duration of each corresponding condition. A graphical representation of the information provided on the screen during each of the conditions is provided in Fig. 1. For the EMG recording of startle responses, 6 acoustic startle probes were delivered per condition, with one half presented during the presence of the cue and the other half during intervals between cues (i.e., during the inter-trial interval, ITI).

There were two recording blocks, each consisting of three N, two P,

[1] Other questionnaires that were administered but not used for the present analyses included the Major Depression Inventory (Olsen, Jensen, Noerholm, Martiny & Bech, 2003), the Multidimensional Existential Meaning Scale (George & Park, 2017), a short form of the Right-Wing Authoritarianism scale (Zakrisson, 2005), an adapted version of the Left-Wing Authoritarianism scale (Altemeyer, 1996), as well as a question about political identity.

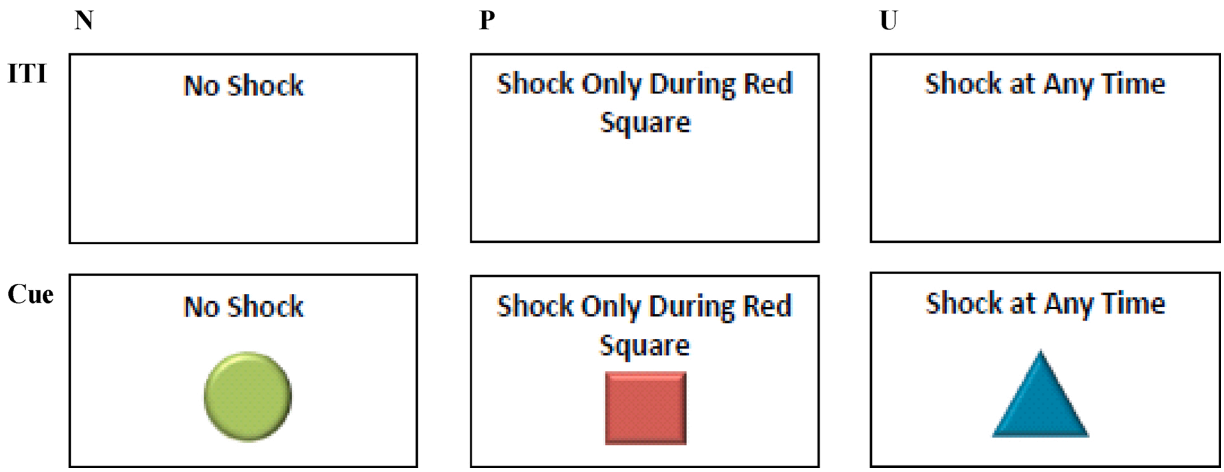

Fig. 1. Information provided on screen during each of the N (no shock), P (predictable shock), and U (unpredictable shock) conditions. Adapted from "Assessing fear and anxiety in humans using the threat of predictable and unpredictable aversive events (the NPU-threat test)" by A. Schmitz and C. Grillon, 2012, *Nature Protocols, 7* (3), 527–532. Copyright 2012 by Springer Nature. Adapted with permission.

and two U conditions. The orders of the two blocks were PNUNUNP and UNPNPNU, and were counterbalanced across participants. Following each block, a series of questions were presented, with two questions pertaining to subjective anxiety felt when the cue was present versus during the ITI in each condition. These questions were answered on a 10-point Likert scale ranging from 1 (*not anxious/ fearful*) to 10 (*extremely anxious/ fearful*). Furthermore, there were three questions concerning the extent to which the shock was experienced as intense, anxiety/fear provoking, and painful, all answered on an individual 10-point Likert scale.

4.4. *Startle recording and processing*

Facial EMG was recorded to assess physiological startle from the orbicularis oculi in accordance with published guidelines (Blumenthal et al., 2005). Before attaching the electrodes, the skin was cleaned carefully. One electrode was attached to the centre of the forehead as a signal ground electrode, and two electrodes were attached below the lower eyelid of the left eye, one below the outer edge and one below the centre of the eye (distance approx. 15 mm). Startle probes were 40-ms, 103 dB bursts of white noise presented binaurally through headphones. Prior to data collection, EMG traces were visually inspected to ensure that blinks could be detected above the noise level in the channel. Startle blink EMG was measured and recorded with TMSi Polybench and processed offline using Aphys. Raw EMG data was filtered using a 28–1000 Hz band-pass filter, rectified, and filtered using a 40 Hz low-pass filter. Peak startle amplitudes were examined within 20–200 ms of startle probe onset. For each trial, EMG activity in the 50-ms baseline period before startle probe onset was averaged and the mean and standard deviation used to determine whether there was a valid startle response. Each trial was also individually manually examined. Trials were rejected (i.e., scored as missing values) if there was excessive noise (mean amplitude > 20 mV) during the baseline period, if the response started before cue onset, or if the response started within 20 ms of cue onset (i.e., minimal onset latency). For accepted trials, a threshold of 7 standard deviations above mean baseline EMG activity was used to determine whether there was a startle response. Trials for which the startle response did not cross the threshold were scored as zero (i.e., non-response), whereas trials for which the response crossed the threshold within 20–200 ms of startle probe onset were scored as valid. For valid responses, peak amplitude of the first high-frequency response within this time window was recorded.

The processed individual responses were used to construct summary scores that could be used in the analyses. First, response amplitude was computed for each trial by subtracting the average amplitude during baseline from the peak startle amplitude. These scores were standardized within subjects (using $T_{ij} = ((\text{raw score}_{ij} - M_i)/SD_i)*10 + 50$) to reduce the influence of participants with a generally large blink response (cf. Nelson & Shankman, 2011), and averaged per condition/cue presence across trials, including values of zero for non-response trials, yielding average startle magnitudes per subject and condition/cue presence (N_{Cue}, N_{ITI}, P_{Cue}, P_{ITI}, U_{Cue}, U_{ITI}) to be used in the analysis of pattern of responses to the NPU-threat test. Finally, potentiation scores were calculated to be used in the main analyses: *Context-potentiated startle* was operationalized as the difference in average startle magnitude between the ITI/cue of the N condition and that during the ITI/cue of the U shock conditions (i.e., $\text{Context}_U = U_{ITI+cue} - N_{ITI+cue}$[2]; cf. Nelson, Liu, Sarapas, & Shankman, 2016). A *fear-potentiated startle* score was also calculated, and was operationalized as the difference in average startle magnitude between the cue of the N condition and that during the cue of the U shock conditions (i.e., $\text{Fear}_p = P_{cue} - \text{Ncue}$) to probe any relationship with cued fear when threat occurrence is uncertain. Split-half reliabilities of the potentiation scores were calculated using potentiation scores for the first and second half of the task, yielding Spearman-Brown coefficients of .725 for Context_u and .607 for Fear_p, which is comparable to what previous studies using potentiated startle have found (e.g., Bradford, Starr, Shackman, & Curtin, 2015).

4.5. *Subjective anxiety ratings*

The subjective anxiety-ratings provided for each condition at the end of each block during the NPU-threat test were also used to construct a summary score. An index of context-potentiated anxiety in response to unpredictability was again constructed ($\text{Anxiety}_U = U_{ITI+cue} - N_{ITI+cue}$) to be used in the main analyses. Split-half reliability analysis yielded a Spearman-Brown coefficients of .772.

4.6. *Procedure*

Participants first read an information sheet describing the study

[2] Because there is some variability in the literature regarding the operationalization of response to uncertainty in this paradigm, we chose to also investigate an alternative way of constructing scores for context-potentiated startle and anxiety in response to uncertainty, $\text{Context}_{U2} = U_{ITI} - N_{ITI}$ and $\text{Anxiety}_{U2} = U_{ITI} - N_{ITI}$, respectively (cf. Nelson & Shankman, 2011). These scores were used to explore correlations with Mindfulness, IU, and anxiety symptoms. Results of these analyses are summarized in footnote 4.

procedure and provided consent to participate. The experimenter orally reviewed and answered questions about the study procedure. Participants began by completing questionnaires administered via computer. Next, electrodes for shock administration were attached to the distal phalanges of the index and middle fingers of the left hand. Furthermore, electrodes for facial electromyography (EMG) were attached. Finally, participants were given earphones for the binaural administration of startle probes. Participants then received an information sheet with a description of the conditions of the NPU-threat test. The lights in the room were dimmed and the test was conducted. Upon completion, participants were debriefed.

4.7. Data analyses

Data analyses were conducted using SPSS 20 for Windows (IBM corporation, Armonk, NY). Two 3 (condition: N, P, U) x 2 (cue, ITI) repeated-measures ANOVAs were conducted to assess whether the uncertainty manipulation in the NPU-threat test yielded the expected startle and subjective responses based on previous research (e.g., Grillon et al., 2008; Schmitz & Grillon, 2012). The Greenhouse-Geisser correction was used to adjust for violation of the sphericity assumption. Next, zero-order correlations were examined to investigate associations among the variables. The mediation hypotheses (2c and 3c) were tested in regression analyses using the PROCESS macro for SPSS (Hayes, 2013). For the present analysis, bias-corrected bootstrap 95 % confidence intervals based on 10,000 bootstrap samples were used for inference about the indirect effect.

5. Results

5.1. Manipulation check: NPU-threat test

Means and standard errors for startle magnitude and subjective anxiety ratings per condition and cue presence are displayed in Fig. 2. For startle magnitude, results of the two-way repeated measures ANOVA revealed main effects for condition, $F(294) = 105.43$, $p < .001$, $\eta_p^2 = .692$, and cue, $F(147) = 80.256$, $p < .001$, $\eta_p^2 = .631$, as well as a condition x cue interaction, $F(1.589,74.691) = 50.091$, $p < .001$, $\eta_p^2 = .516$. The interaction was followed up by conducting repeated measures ANOVAs (condition: N, P, U) at each level of cue (cue and ITI). During the ITI, startle magnitudes differed significantly between conditions, $F(294) = 36.911$, $p < .001$, $\eta_p^2 = .440$, with pairwise comparisons showing that startle magnitudes were greater in the P ($p = .001$) and U ($p < .001$) conditions, compared to the N condition, and greater in the U relative to the P condition ($p < .001$). These findings are in line with the expected pattern of results, as an unpredictable context (i.e., ITI, not cued) has been shown to be more anxiogenic than a predictable context, which in turn is more anxiogenic than a non-threatening context (Schmitz & Grillon, 2012). Similarly, during the cue, startle magnitudes differed significantly between conditions, $F(1.620, 76.123) = 113.112$, $p < .001$, ${}^2_p = .706$, such that startle magnitudes in the P ($p < .001$) and U ($p < .001$) conditions were again greater relative to the N condition. Here, startle magnitude was greater in the P relative to the U condition ($p = .001$). This is consistent with a large fear-potentiated response to the cue when electrical stimulation is expected and has also been reported in previous research (e.g., Grillon et al., 2008).

For subjective anxiety ratings, results of the two-way repeated measures ANOVA again revealed main effects for condition, $F(1.479,69.506) = 115.340$, $p < .001$, $\eta_p^2 = .710$, and cue, $F(1,47) = 57.889$, $p < .001$, $\eta_p^2 = .552$, as well as a condition x cue interaction, $F(1.343,63.113) = 62.579$, $p < .001$, $\eta_p^2 = .571$. Repeated measures ANOVAs at each level of cue revealed that during the ITI, subjective anxiety ratings differed significantly between conditions, $F(1.666,78.287) = 94.152$, $p < .001$, $\eta_p^2 = .667$, with greater anxiety ratings in the P ($p < .001$) and U ($p < .001$) conditions, relative to the N condition, as well as greater anxiety ratings in the U condition ($p < .001$), relative to the P condition, paralleling the findings from the startle data and consistent with expectations. Similarly, during the cue, subjective anxiety ratings differed significantly between conditions, $F(1.432,67.286) = 127.285$, $p < .001$, $\eta_p^2 = .730$, with greater anxiety ratings in the P ($p < .001$) and U ($p < .001$) conditions, relative to the N condition, and greater anxiety ratings in the U condition ($p = .001$), relative to the P condition, which is again consistent with unpredictable threat being more anxiogenic, compared to predictable threat or no threat.

5.2. Descriptives and correlation analyses

Following examination of histograms, normal qq-plots, skewness- and kurtosis- statistics, it was determined that the distribution of the variables did not exhibit substantial deviations from normality[3] . Correlations between all variables as well as means and standard deviations are summarized in Table 1.

Concerning hypothesis (1), FFMQ scores were inversely related with scores on all measures of anxiety symptoms, with correlations ranging from −.27 to −.67 ($ps < .05$). Furthermore, in line with hypothesis (2a), FFMQ scores were inversely related with IUS scores ($rs = -.53$ to $-.61$, $p < .05$), and IUS scores were significantly associated with most anxiety symptom measures ($rs = .29$–$.66$, $ps < .05$), largely yielding support for hypothesis (2b). Only the relationship between IUS scores and interoceptive fear was not significant ($rs = .01$–$.14$, $ps = .30$). Concerning IUS subscales, correlations with FFMQ scores as well as anxiety measures (with the exception of interoceptive fear) were significant and largely comparable (see Table 1).

Concerning hypothesis (3a), FFMQ scores were not significantly related with response to uncertainty in the NPU-threat test, assessed by self-report anxiety ($r = -.176$, $p = .232$) and startle ($r = .073$, $p = .622$) potentiated by an unpredictable context. This is at odds with our predictions and indicates that, in this sample, mindfulness was not related to physiological or subjective responses potentiated by an unpredictable threat-context (i.e., change in startle magnitude/ subjective anxiety from cue/ITI during the N condition to cue/ITI during the U condition). Moreover, and contrary to the predictions made in hypothesis (3b), context-potentiated responses were not significantly associated with any anxiety measure ($rs = -.024$ to $.256$, $ps > .07$).

Correlation analyses additionally show that context-potentiated response to uncertainty in the NPU task was unrelated with IUS scores, including when NPU-task response to uncertainty is assessed with startle ($rs = -.144$ to $-.187$, $ps > .20$) or self-report anxiety ($rs = -.006$ to $.012$; $ps > .93$).[4] These results suggest that the self-report and physiological measures of response to uncertainty do not seem to both measure an underlying construct of emotional reactivity to uncertainty.

5.3. Mediation analyses

Based on the correlation findings, self-report IU (but not the NPU-test measures of context-potentiated startle and self-report anxiety) was investigated as a mediator for the relationship between mindfulness and anxiety symptoms. The mediation hypothesis for each outcome variable was tested in PROCESS by regressing individual anxiety measures on the

[3] A small number of outliers were detected on the APPQ agoraphobia subscale ($n = 1$) and the APPQ interoceptive subscale ($n = 2$). All analyses involving the respective variables were repeated with imputed values for these cases that were one unit above the next extreme value (Tabachnick & Fidell, 2007), which slightly improved skewness and kurtosis statistics for agoraphobia. However, results did not change significantly.

[4] Analyses of the alternative scoring method for context-potentiated startle and anxiety in response to uncertainty (i.e., $Context_{U2}$ and $Anxiety_{U2}$) revealed no significant correlations with mindfulness, IU, or anxiety ($ps > .05$).

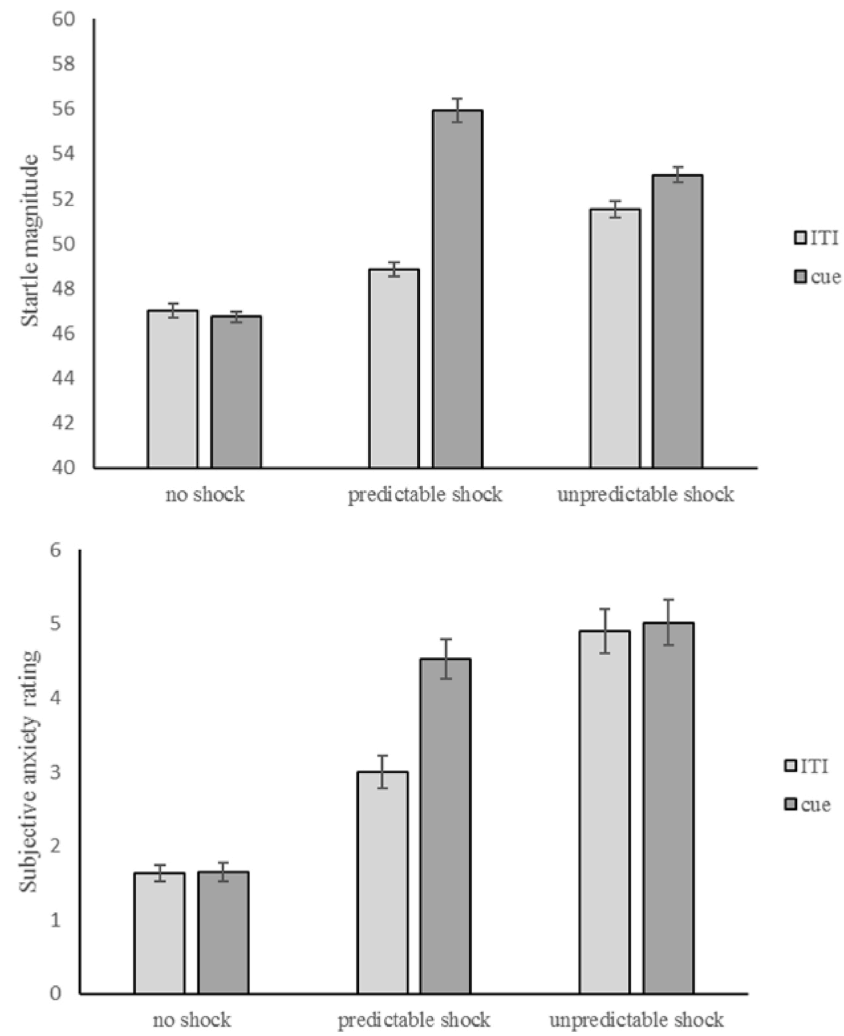

Fig. 2. Startle magnitude and subjective anxiety ratings per condition and cue presence. Error bars represent standard error.

Table 1
Intercorrelations, means, and standard deviations for all variables.

	1.	2.	3.	4.	5.	6.	7.	8.	9.	11.	12.	13.	*M*	*SD*
1. FFMQ	–												74.434	13.348
2. APPQ-S	−.652**	–											17.736	12.056
3. APPQ-A	−.516**	.582**	–										12.132	8.272
4. APPQ-I	−.268*	.121	.524**	–									4.151	4.439
5. PSWQ	−.671**	.515**	.532**	.219	–								53.793	13.348
6. OCI-R	−.328*	.172	.259	.194	.412**	–							17.189	9.863
7. IUS	−.614**	.402**	.434**	.092	.656**	.622**	–						31.925	9.967
8. IUS-P	−.527**	.288*	.370**	.138	.568**	.625**	.934**	–					19.359	6.313
9. IUS-I	−.598**	.469**	.426**	.008	.632**	.481**	.870**	.636**	–				12.566	4.668
11. $Anxiety_U$	−.176	.127	.256	.191	.036	.057	.011	.012	.006	–			3.521	2.043
12. $Context_U$	.073	.075	−.024	−.018	−.123	−.242	−.186	−.187	−.144	.150	–		5.423	2.917
13. $Fear_P$	−.235	.176	.199	.145	.272	−.109	.005	−.077	.110	.238	.229	–	7.052	4.644

Note: FFMQ, five facet mindfulness questionnaire; APPQ, albany panic and phobia questionnaire; APPQ-S, social anxiety subscale; APPQ-A, agoraphobia subscale; APPQ-I, interoceptive fear subscale; PSWQ, penn state worry questionnaire; OCI-R, obsessive compulsive inventory – revised; IUS, intolerance of uncertainty scale; IUS-P, prospective subscale; IUS-I, inhibitory subscale; $Anxiety_U$, subjective anxiety potentiation: unpredictable context; $Context_P$, startle potentiation: predictable context; $Context_U$, startle potentiation: unpredictable context; $Fear_P$, startle potentiation: predictable condition, cue present. *$p < .05$; **$p < .01$.

FFMQ, and entering IU as a potential mediator. Results are summarized in Table 2. As expected based on the zero-order correlation, the effect of mindfulness on IU was significant, with higher levels of mindfulness predicting lower levels of IU. Regarding social anxiety and agoraphobia symptoms, the total effect of mindfulness on both outcome variables was significant, with higher levels of mindfulness predicting lower levels of both social anxiety and agoraphobia symptoms. In the full model, when controlling for mindfulness, adding IU did not account for significant additional variance in either symptoms of social anxiety or agoraphobia, and the indirect effect (a*b) in both cases yielded a bias-corrected bootstrap CI that included zero. This indicates that, contrary to our predictions, IU did not mediate the relationship with symptoms of either social anxiety or agoraphobia. We conducted post-hoc power analyses using Monte Carlo Power Analysis for Indirect Effects (Schoemann,

Table 2
Results of the mediation analyses: test of the effect of mindfulness on anxiety through IU.

Outcome variable	Total effect	Direct effect	Indirect effect (95 % CI)
APPQ-s	−.594(.095)**	−.592(.121)**	−.0015 (−.182, .169)
APPQ-A	−.329(.075)**	−.256(.094)**	−.1153 (−.298, .079)
PSWQ	−.677(.103)**	−.434(.120)**	−.241 (−.404, −.097)
OCI-R	−.248(.098)*	.066(.103)	−.415 (−.592, −.265)

Note. APPQ, albany panic and phobia questionnaire; APPQ-S, social anxiety subscale; APPQ-A, agoraphobia subscale; PSWQ, penn state worry questionnaire; OCI-R, obsessive compulsive inventory – revised; CI, Bias-corrected bootstrap 95 % Confidence Interval; *$p < .05$; **$p < .01$.

Boulton, & Short, 2017), which showed that the power for detecting indirect effects for both social anxiety (power = .06) and agoraphobia (power = .26) symptoms was very small. A different picture emerged for worry and obsessive-compulsive symptoms. Again, the total effect of mindfulness on both outcome measures was significant, with higher levels of mindfulness predicting lower levels of worry and obsessive-compulsive symptoms. This time, adding IU to the model did account for significant additional variance in both outcome variables, and the bias-corrected bootstrap CI for the indirect effect did not include zero in both cases, indicating that IU mediated the effect of mindfulness on both worry and obsessive-compulsive symptoms. For obsessive-compulsive symptoms, when controlling for IU in the full model, the direct effect of mindfulness was diminished to non-significance, while for worry, the effect of mindfulness reduced but remained significant. Thus, IU partially mediated the effect of mindfulness on worry symptoms and fully mediated the effect of mindfulness on obsessive-compulsive symptoms. Here, post-hoc power analyses revealed that the power for detecting indirect effects for both worry (power = .89) and OCD symptoms (power = .99) was high.

6. Discussion

The present study examined whether reactivity to uncertainty statistically mediates the inverse relation between mindfulness and anxiety symptoms. Based on research showing that intolerance of uncertainty (IU) plays a central role in anxiety (Boswell et al., 2013; Chen & Hong, 2010), and the premise that mindful acceptance involves letting go of attempts to change one's experience, we proposed that emotional reactivity to uncertainty may represent one potential mechanism responsible for the relationship between mindfulness and anxiety symptoms. The aim of the present study was to extend evidence for these relationships by measuring reactivity to uncertainty via self-report (the IU scale) and in a threat-of-shock paradigm that manipulates the predictability of a threat. We predicted (1) that mindfulness would be inversely related to measures of anxiety symptoms, (2a)[3a] that mindfulness would be inversely related to uncertainty measured by self-report IU [the NPU-threat test], (2b)[3b] that anxiety symptoms would be positively related to uncertainty measured by self-report IU [NPU-threat test], and (2c)[3c] that the relation between mindfulness and anxiety symptoms would be statistically mediated by uncertainty measured by self-report IU [NPU-threat test].

Regarding hypothesis (1), in line with predictions, mindfulness was inversely related to all measures of anxiety symptoms (i.e., social anxiety, agoraphobia, interoceptive fear, worry, and obsessive-compulsive symptoms). This supports previous findings of an inverse relationship between mindfulness and anxiety (Baer et al., 2006; Ostafin et al., 2014), and warrants more experimental research investigating whether changes in mindfulness are associated with subsequent changes in symptoms of a range of anxiety disorders. This would allow for stronger causal inferences about the potential usefulness of mindfulness in alleviating anxiety symptoms.

6.1. Intolerance of uncertainty

In line with hypothesis (2a), supporting previous research (Kraemer et al., 2016), mindfulness was significantly inversely related to IU, lending support to the idea that mindfulness is associated with acceptance of experience. Future experimental studies are needed to investigate whether IU decreases over the course of mindfulness interventions to corroborate this evidence and permit causal statements.

Mostly in support of hypothesis (2b), IU was significantly associated with most measures of anxiety symptoms, with the exception of interoceptive fear. This last finding is surprising, as previous research has shown consistent relations between IU and interoceptive fear as measured with the anxiety sensitivity index (ASI-3; e.g., Hong, 2013). The ASI-3 measures fear of sensations associated with anxiety with items on three subscales, reflecting physical, cognitive, and social concerns (Taylor et al., 2007). The 'physical concerns' subscale may be a better measure of interoceptive fear than the APPQ interoceptive fear subscale. Non-significant associations of the APPQ interoceptive fear subscale with IU and most anxiety symptoms are in line with previous criticism of the subscale in terms of construct validity. The items seem to mainly address strenuous physical activity and neglect fear of bodily sensations per se (Brown, White, & Barlow, 2005). In contrast, items on the 'physical concerns' subscale of the ASI-3 address this dimension (e.g., "It scares me when my heart beats rapidly"). Indeed, the physical concerns facet of anxiety sensitivity has been shown to be particularly elevated in panic disorder (Taylor et al., 2007), and also has previously been related to IU (Carleton, Collimore, & Asmundson, 2010), as well as a range of other anxiety disorders (OCD, generalized anxiety, social anxiety; Taylor et al., 2007). Future research could thus benefit from assessing the proposed relationships with a different measure of interoceptive fear such as the physical concerns subscale of the ASI-3.

Concerning the other measures of anxiety symptoms, mediation analyses revealed that, in line with hypothesis (2c), IU partially statistically mediated the relationship of mindfulness with worry and fully mediated that with obsessive-compulsive symptoms. However, no support was found for an indirect effect on social anxiety and agoraphobia symptoms.

One possible explanation for this combination of mediation results is, as noted above, that our measurement of social anxiety and agoraphobia with the APPQ may have impacted these associations. Similar to the interoceptive fear subscale described above, the social anxiety and agoraphobia subscales are limited to descriptions of situations that may be anxiety-inducing to someone with social anxiety (e.g., "meeting strangers") or agoraphobia (e.g." driving on highways"), but neglect specific assessment of other characteristics of these anxiety symptoms such as fear of negative evaluation in social anxiety or fear of helplessness associated with some anxiety-inducing situations in agoraphobia. It is thus difficult to draw conclusions from these results, and future research should employ more comprehensive scales for these symptom groups when assessing these relationships.

Additionally, collinearity between the predictors (i.e., mindfulness and IU) may have diminished the power in the present sample (a) for teasing apart individual effects, and in turn (b) for detecting a significant indirect effect. In multiple linear regression, it is difficult to discriminate effects of individual predictors if these are strongly correlated. Specifically, estimates of individual effects ignore the shared variance between predictors, and thus the effective amount of information used is reduced (Baguley, 2012). In the present sample, mindfulness explained 40 % of the variance in IU, meaning that only 60 % of the available information was used for the estimation of individual effects. This is problematic, as this loss of information reduces the effective sample size and inflates the error variance for individual effects (Baguley, 2012). Moreover, a large coefficient relating the independent variable to the mediator also increases the error variance of the indirect effect, making it more likely that zero will be contained in bootstrap confidence intervals, a problem that is enhanced when the coefficient relating the mediator to the outcome variable is substantially smaller (Beasley, 2014). For the present study, this could mean that the strong relationship between IU and mindfulness may have hampered the detection of small effects. Given that in the present sample IU was less strongly related to symptoms of social anxiety and agoraphobia than to worry and obsessive-compulsive symptoms, the relatively smaller coefficient relating the mediator to the outcome in these cases may have enhanced this problem further.

An alternative explanation for the mediation results may be a particular importance of IU in the relationships of mindfulness with worry and OCD symptoms, compared to social anxiety and agoraphobia symptoms. While associations between IU and worry/OCD symptoms are especially strong in our sample, it is unlikely that this combination of results is explained by IU being specifically relevant to worry and OCD symptoms, as there is strong evidence from previous research that IU plays a comparably large role across anxiety disorders, although relations with symptoms of GAD are generally stronger (McEvoy et al., 2019). However, based on the present results, it is possible that a specific role in the relationship between mindfulness and worry/OCD symptoms can be attributed to IU. Worry in GAD and thought-control strategies for obsessions in OCD are suggested to share the common underlying function of reducing distress associated with the perception of uncertainty regarding a wide range of potential threats, and the two disorders are highly comorbid (Fergus & Wu, 2010; Pallanti, Grassi, Sarrecchia, Cantisani, & Pellegrini, 2011). One factor differentiating the two disorders is thought to be the strategy employed to reduce uncertainty (Shahjoee, Aliloo, Roodsari, & Fakhari, 2012), although worry has also been found to be one thought-control strategy in OCD (Fergus & Wu, 2010). Both of these disorders thus involve a pervasive preoccupation with and attempts to avoid uncertain future threat. Central elements of mindfulness involve a focus on the present moment and acceptance of (even unpleasant) experience, both of which are antithetical to these future-oriented symptoms of OCD and GAD. It is conceivable that IU may account for this inverse relation to GAD and OCD symptoms and it is a possibility that for these reasons, IU plays a larger role here than in the mindfulness-symptom relationship for social anxiety and agoraphobia, for which other factors may be more important.

Nevertheless, the present study provides evidence that IU may statistically mediate the effect of mindfulness on symptoms of some anxiety disorders. Future research should investigate the proposed relationships in larger samples to allow for sufficient power to detect unique and indirect effects and should employ more comprehensive measures of panic and social anxiety symptoms. Moreover, experimental research investigating these variables over the course of a mindfulness intervention is warranted to allow for causal inferences about the potential for IU to have a mechanistic role in the mindfulness-anxiety relationship.

6.2. Reactivity to unpredictable threat

With regard to startle and subjective anxiety in the context of unpredictable threat, a different picture emerged. Inconsistent with predictions (3a-c), mindfulness was not related to the context-potentiated responses towards unpredictable threat assessed by startle and self-report anxiety. Furthermore, context-potentiated response to unpredictable threat was neither related to symptoms of anxiety nor to individual differences in IU.

The lack of significant associations between the threat-of-shock task, including context-potentiated startle and subjective anxiety, and the IU scales suggest that the two measures did not assess reactivity to uncertainty in the present study. The non-significant association between the threat-of-shock task and the prospective (i.e., cognitive/emotional) facet of IU is especially surprising, as these measures have most theoretical overlap as assessing adverse emotional responses in anticipation of uncertainty. One potential explanation for this finding is that the self-report IU scale and the startle response to unpredictable threat measure different-level processes, with the IU scale measuring a higher-order cognitive process in comparison to startle, which measures a lower-order defensive response to uncertainty. In theoretical work on emotional consciousness, LeDoux and colleagues argue that lower-order responses can contribute to, but are not necessary for, the conscious experience of any emotional cognitive state (LeDoux & Brown, 2017; LeDoux & Hofmann, 2018). Thus, the IU scale may tap a higher-order cognitive emotional state that does not necessarily relate with a lower-order defensive response such as startle. An alternative explanation for the non-significant association may be that the nature of the uncertainty manipulation may not sufficiently mimic the uncertainties encountered in real life which are addressed with IU.

Regarding the relationship between responses to unpredictable threat and IU, previous research has shown mixed results. Chin et al. (2016) showed correlations between IU and both startle potentiation and subjective anxiety in the context of threat uncertainty, whereas other research has not found an association between IU and startle potentiation or subjective responses in an unpredictable threat-context (Bennett, Dickmann, & Larson, 2018; see Tanovic, Gee, & Joormann, 2018 for a recent review of the relationship between IU and startle). Further, Nelson and colleagues have conducted research with the individual IU subscales to detect possible suppressor effects and have found a negative association between startle in response to unpredictable threat and inhibitory IU, and a positive association with prospective IU, suggesting that the IU subscales may reflect hyper-reactive (prospective IU) and inhibitory (inhibitory IU) manifestations of IU (Nelson & Shankman, 2011; Nelson et al., 2016). We did not examine mutual suppressor effects, given the high collinearity between the two IU subscales and the relatively small sample. It should be noted that most of the studies described above used small samples, rendering any detected effects vulnerable to being unreliable. This, taken together with methodological variation in threat-of-shock tasks across previous studies, calls for future studies investigating how methodological differences in the NPU-task design impact perceived uncertainty and the relationship between startle and IU scores.

Our findings that the threat-of-shock task was unrelated to symptoms of anxiety contrasts with previous research showing that specific phobia, social anxiety, and panic disorder were associated with greater startle-potentiation in response to uncertain threat (Gorka, Lieberman, Shankman, & Phan, 2017; Grillon et al., 2008). The non-significant findings were particularly unexpected from the perspective that the threat task showed patterns of responses to predictable and unpredictable threat similar to previous research (Schmitz & Grillon, 2012). As previously mentioned, the relatively small sample size in the current study is one potential reason for the non-significant findings. Thus, future studies with an unpredictable threat task should include larger samples.

6.3. Limitations

A number of limitations must be considered when interpreting the non-significant results with regard to relationships between physiological and subjective potentiated responses from the NPU-threat test and individual difference variables assessing mindfulness, anxiety symptoms, and IU. As addressed above, the sample size in the present study was somewhat small. The study's power to detect relations with the NPU startle response may have been especially insufficient, given the relatively higher response variability (due to noise or other influences) in psychophysiological measures.

In addition, some methodological considerations regarding the threat-of-shock task should be considered. First, over the course of the task, a total of six shocks were delivered in the U condition, compared to four shocks during the P condition, a difference which could have affected the aversiveness of the different conditions. However, the pattern of responses to the different conditions closely matches that of previous research where the number of shocks was matched in the P and U conditions, rendering this option unlikely (e.g., Schmitz & Grillon, 2012). Additionally, regarding subjective responses, assessing self-report anxiety in response to uncertainty only after each block instead of online could have caused recall bias. However, we chose not to use an online measure of anxiety because paying attention to reporting on emotional experience could alter the experience and response to the threat-of-shock task, which could limit the validity of the startle assessment. Justifying this decision, online and offline measures that take place soon after the experience have been found to be strongly correlated (Mauss, Levenson, McCarter, Wilhelm, & Gross, 2005).

Furthermore, regarding relationships with anxiety symptoms, the present sample consisted of students who were not recruited for elevated anxiety levels. Notably, the studies that found relationships between threat-of-shock tasks and anxiety disorders used clinical samples in comparison to healthy controls. This opens the possibility that a restriction of range may have hampered the detection of small effects in the present study. A valuable avenue for future research would thus be to examine these relationships in sufficiently powered samples with heightened symptom levels on multiple anxiety dimensions.

Finally, regarding the analysis of IU as a mediator for the mindfulness-anxiety relationship, it should be considered that the present study was correlational. Future research should evaluate the causal nature of these relationships in intervention studies, which will also enable assessment of the temporal precedence of the mediator. Furthermore, using larger samples here will also weaken the limiting effect that collinearity between mindfulness and IU may have on power to detect unique and indirect effects.

6.4. Conclusions

In summary, the present results provide initial evidence that IU may play a role in the relationship between mindfulness and anxiety symptoms across multiple disorders. Furthermore, the present study was the first to investigate a possible relation between mindfulness and reactions to uncertainty in a threat-of-shock paradigm. Although here associations between context-potentiated responses to unpredictable threat and mindfulness, anxiety symptoms, and IU were non-significant, future research is warranted and should investigate these relationships in larger samples and with intervention studies.

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Declaration of Competing Interest

None

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