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Published in:
International Journal of Psychophysiology

DOI:
10.1016/j.ijpsycho.2022.06.014

Publication date:
2022

International Journal of Psychophysiology 179 (2022) 30–42

Contents lists available at ScienceDirect

International Journal of Psychophysiology

journal homepage: www.elsevier.com/locate/ijpsycho

Aversive response to uncertainty as a mediator for the effect of a mindfulness intervention on symptoms of anxiety

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ARTICLE INFO

Keywords:
Anxiety
Mindfulness
Intolerance of uncertainty
Unpredictable threat
Startle

ABSTRACT

Theoretical background: Intolerance of uncertainty plays a central role in anxiety and research suggests that it's an important treatment target. Investigating response to uncertainty using other dimensions than self-report, such as physiological responses, can further the effort to understand the role of uncertainty in anxiety more fully. Mindfulness interventions have become increasingly interesting in their application to anxiety, as they foster acceptance of unpleasant aspects of experience. The aims of the study were to examine whether a mindfulness intervention reduced response to uncertainty and anxiety symptoms, and to examine the associations between intolerance of uncertainty, physiological response to uncertainty, mindfulness and anxiety.

Methods: Participants were 117 students who completed a two-week mindfulness or audiobook control intervention. At pre- and post-intervention assessments, measures of anxiety, mindfulness, and intolerance of uncertainty were completed and a threat-of-shock task assessing startle responding to unpredictable shock was administered.

Results: Findings showed a significant effect of the intervention for social anxiety symptoms. Furthermore, intolerance of uncertainty mediated the effect of the intervention on symptoms for social anxiety and worry. No such effects were found for physiological response to uncertainty.

Conclusion: The study adds to the understanding of the role of response to uncertainty in anxiety as well as to its mechanistic role in the context of mindfulness practice. Implications and possible explanations for the non-significant main effects of the intervention on anxiety symptoms and physiological response to uncertainty are discussed.

1. Introduction

Uncertainty has been described as a situation in which something is unknown (Cambridge Advanced Learner's Dictionary and Thesaurus, 2013) or as the experiential state of not being sure what will happen (Cambridge business English dictionary, 2011). Given that it is rarely possible to predict with absolute certainty what will happen and when it will happen, uncertainty is inherent in virtually everything that lies in the future. As such, uncertainty has long been thought to be critically involved in anxiety, which has been defined as a future-oriented emotion characterized by adverse anticipatory responding to potential threat. Indeed, uncertainty has been included in a number of theoretical models of anxiety (e.g., Barlow, 2002; Carleton, 2016a, 2016b; Hirsh et al., 2012). Although anxiety can be adaptive by preparing the organism for threats, anxiety can also be maladaptive when the response is out of proportion to the probability of the threat actually occurring, the magnitude of the actual consequences, or both (Grupe and Nitschke, 2013). The degree of sensitivity to uncertainty is one characteristic that has been proposed to determine whether anxiety becomes maladaptive and clinically relevant (Grupe and Nitschke, 2013) and Carleton (2016a, 2016b) has suggested that fear of the unknown is the fundamental fear underlying anxiety disorders. Recent research has begun to provide empirical evidence to corroborate the central role that response to uncertainty plays in anxiety (McEvoy et al., 2019; Papenfuss and Ostafin, 2021; Tanovic et al., 2018). Given that uncertainty cannot be eliminated from life and that it is central to anxiety disorders, it has been suggested that interventions that focus on developing acceptance of and strategies to cope with uncertainty may be worthwhile tools in the treatment of

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https://doi.org/10.1016/j.ijpsycho.2022.06.014
Received 31 January 2022; Received in revised form 13 June 2022; Accepted 20 June 2022
Available online 24 June 2022

anxiety (Grupe and Nitschke, 2013; Lohr et al., 2007).

Over the past decades, the most prominent construct assessing individual differences in response to uncertainty has been *intolerance of uncertainty* (IU). IU has most recently been defined as "an individual's dispositional incapacity to endure the aversive response triggered by the perceived absence of salient, key, or sufficient information" (Carleton, 2016a, 2016b, p. 31). A corresponding scale assesses response to uncertainty with two facets, prospective IU and inhibitory IU, respectively representing adverse anticipatory cognitive and emotional processes related to future uncertainty as well as behavioral inhibition in response to immediate confrontation with uncertainty (Carleton et al., 2007; McEvoy and Mahoney, 2011). Initially, IU was thought to be mainly involved in generalized anxiety disorder (GAD). It was argued to facilitate a focus on a variety of potential threats and thereby cause the "what if…?" thoughts typical of worry that serve the aim of reducing the experience of uncertainty (Dugas et al., 1998). Research has since shown that in addition to GAD, IU also plays an important role in other types of anxiety such as social anxiety, panic, and agoraphobia symptoms as well as obsessive-compulsive symptoms (McEvoy et al., 2019). Moreover, two lines of evidence suggest that IU may represent an important treatment target. First, IU has been shown to be a vulnerability factor that temporally precedes the development of symptoms. For example, prospective research shows that IU interacts with life stress to predict anxiety symptoms (Chen and Hong, 2010). Second, a number of studies suggest that IU is malleable and therefore a potential treatment target: For instance, research has shown that IU and related biases can be reduced through IU-focused Cognitive Bias Modification training (Oglesby et al., 2017). Moreover, IU has been found to decrease over the course of different interventions within the cognitive-behavioral therapy (CBT) approach such as the transdiagnostic Unified Protocol (Boswell et al., 2013), transdiagnostic group CBT for anxiety (Talkovsky and Norton, 2016), metacognitive therapy for GAD (McEvoy and Erceg-Hurn, 2016), or imagery-enhanced CBT for social anxiety (McEvoy and Erceg-Hurn, 2016). These reductions in IU have been found to be related to reduced symptom levels across anxiety disorders following treatment (Boswell et al., 2013; Talkovsky and Norton, 2016; McEvoy and Erceg-Hurn, 2016). Moreover, research has shown that reductions in IU over the course of CBT treatment were related to reduced functional impairment and increased coping efficacy (Palitz et al., 2019). In sum, findings corroborate IU as a vulnerability factor of anxiety, and substantiate the suggestion that IU is an important treatment target. Thus, optimizing treatment to maximize effects on IU may improve treatment outcomes and is therefore an important avenue for research.

Studies investigating the role of IU in anxiety and its treatment have mostly used self-report assessments of intolerance of uncertainty. Although self-report measures provide important information, their usefulness can also be compromised by processes such as participants having poor introspective abilities or misunderstandings of the target constructs (Demetriou et al., 2014). In response, there have been efforts to develop additional measures that are less reliant on self-report, such as indirect measures based on psychophysiology or behavioral response (Grillon et al., 2004; Lommen et al., 2010). Such multi-modal assessment approaches can help foster a more complete understanding of how uncertainty relates to anxiety. One indirect approach uses threat-of-shock tasks in which uncertainty is modeled by manipulating the predictability of shock occurrence or timing. Physiological indices of anxious arousal administered under conditions of unpredictable shock may then provide information regarding the relation between IU and anxiety symptoms. Specifically, physiological reactivity under conditions of unpredictable threat is proposed to represent an extended state of anxious anticipation created by the inability to predict periods of safety. In contrast, physiological reactivity to predictable threat (e.g., a cue signals the onset of shock) represents a brief fear response caused by the expectation of immediate threat (Grillon et al., 2004).

Previous research has reliably shown a relation between such physiological measures of response to uncertainty and a number of anxiety symptoms, with studies showing positive relations with social anxiety disorder, specific phobia, and panic disorder (Grillon et al., 2008; Gorka et al., 2017a; Gorka et al., 2017b). However, no such relation has been found with GAD symptoms (Gorka et al., 2017a; Grillon et al., 2009). One potential explanation for the discrepant findings may be found in a recent proposed distinction between GAD symptoms as being largely characterized by distress/misery, in contrast to other anxiety disorders, which have been classified as being characterized by symptoms that are based in fearful responding (Clark and Watson, 2006). Indeed, there seems to be considerable variability in startle potentiation across anxiety psychopathology along the fearful versus distress/misery dimension, with increased startle modulation found in fear-based disorders such as specific phobias and blunted startle found for distress/misery-based disorders such as GAD (Lang et al., 2016). Also in line with this distinction, GAD symptoms have been shown to be related to suppression of autonomic arousal, which may partly reflect differential findings on a physiological level of response to uncertainty (Brown et al., 1998). However, more research is needed to continue to explore these differential relationships.

The evidence regarding the relation between physiological and self-report measures of response to uncertainty has been more mixed. For example, while some studies have shown a positive relation between startle in the context of unpredictable threat and self-report IU (Chin et al., 2016), others have found no relation (Bennett et al., 2018; Papenfuss et al., 2021), while still others have shown a negative relation (Nelson and Shankman, 2011). In addition, other research has shown that rather than being related to startle reactivity under conditions of unpredictable threat, IU was related to startle during periods of certain safety from shock (Lieberman et al., 2016).The heterogeneity in results regarding the relation between startle in the context of uncertain threat and self-report IU may also be due to the predominant use of small samples which make results less reliable, as well as due to methodological differences such as the exact uncertainty manipulation or the operationalization of response to uncertain threat, which could influence findings. Thus, research should further investigate these relations in sufficiently large samples and also explore the role of methodological differences.

Mindfulness-based interventions represent a category of treatment that may have particular promise in reducing aversive response to uncertainty and, subsequently, anxiety symptoms. Mindfulness has been defined as consisting of awareness of the present-moment experience and a non-judgmental and accepting attitude toward that experience (Bishop et al., 2004). As such, mindfulness interventions may be well-suited in the treatment of disorders that are characterized by intolerance of specific aspects of experience (Bishop et al., 2004). One way in which mindfulness may be helpful is that it involves training attention to focus on the present, which could help to prevent tendencies to orient to the future with concomitant anxious apprehension. In addition, as the non-judgmental element involves "a conscious decision to abandon one's agenda to have a different experience" (Bishop et al., 2004, p. 233), mindfulness responses to uncertainty may facilitate a response of simply observing and accepting (allowing) impulses to escape the experience rather than automatically acting on those impulses. In this way, the aversive nature of uncertainty may remain, but it is no longer a problem that needs to be fixed through avoidance and escape. Furthermore, by practicing non-judgmental awareness, individuals may learn that they can cope with uncertainty – that it is something that, while unpleasant, does not necessarily lead to overwhelm but instead just comes and goes – and successful coping experiences may further facilitate acceptance of aversive uncertainty. The reduction of aversive response to uncertainty, then, represents one way in which mindfulness could reduce symptoms of anxiety.

Indeed, psychological interventions based on mindfulness have been shown to be effective in the treatment of anxiety (Abreu Costa et al., 2018). Although the mechanisms of the effect of mindfulness interventions on anxiety remain unclear, response to uncertainty has

promise for the reasons noted above. Initial research regarding the mediating effect of IU has been promising: In two cross-sectional studies, IU statistically mediated the relation between mindfulness and different anxiety symptoms: the inverse relation between mindfulness and anxiety symptoms was partially accounted for by IU, which was inversely related to mindfulness and positively related to anxiety (Kraemer et al., 2016; Papenfuss et al., 2021). Moreover, initial intervention research has also shown that IU decreased over the course of a mindfulness intervention in a sample of patients with obsessive-compulsive disorder (Mathur et al., 2021) as well as a sample of men diagnosed with prostate cancer (Victorson et al., 2017). To corroborate and extend this initial evidence to a range of anxiety symptoms and directly evaluate the mediating role of IU, experimental research examining the mediating effects in the context of an intervention is needed. In contrast to the small but growing research on mindfulness and the self-report IU measure, we are aware of only one study examining the relation between mindfulness and physiological response to uncertainty. This research used a cross-sectional design to examine the relationship between mindfulness and startle in the context of uncertain threat in a threat-of-shock task (Papenfuss et al., 2021). Although no significant associations were found between trait mindfulness and physiological response to uncertainty, the study had a relatively small sample and thus the statistical power was suboptimal.

The main aim of the study was thus to extend and corroborate previous research by Papenfuss et al. (2021) and Mathur et al. (2021) by examining whether a two-week mindfulness intervention could reduce response to uncertainty as well as anxiety symptoms, compared to a control intervention. The study extends previous research in the following ways: (1) by using an experimental design to evaluate the mediating role of IU for the effect of mindfulness on anxiety in the context of an intervention, (2) by investigating whether a mindfulness intervention can similarly affect aversive physiological responding to uncertainty, and (3) by examining these questions with a sample size that provides better statistical power than previous studies. In a preliminary correlation analysis of pre-treatment scores, the associations between self-reported intolerance of uncertainty and response to uncertainty in a threat-of-shock task, as well as between these parameters and trait mindfulness and anxiety symptoms were examined to initially explore the proposed relations cross-sectionally. To address the main aim of the study, we hypothesized that the mindfulness intervention would (I) reduce anxiety symptoms and (II) reduce the strength of response on self-report and physiological measures of response to uncertainty, and (III), that the reductions in anxiety symptoms would be mediated by self-report and physiological responses to uncertainty.

2. Material and methods

2.1. Participants

Participants were 150 undergraduate psychology students (70.66 % Female, M_{age} = 22.05, SD_{age} = 4.23) recruited through the first-year participants pool and for whom participating in the study counted toward fulfillment of program requirements. This sample size was determined prior to the start of data collection and was based on a priori power analysis (using medium effect size) and accommodating for approximately 15 % drop-out/data exclusions to prevent loss of power. A majority of the sample were from the Netherlands (26 %) or Germany (32.7 %), with the remaining 41.3 % indicating other nationalities. Taking an experimental psychopathology approach, we only included participants in the analysis who completed a minimal dose of the intervention. A precondition to be included in the analyses was thus completion of 50 % of the intervention. Of the initially recruited participants, 33 (of which 18 were in mindfulness condition) were excluded because they indicated completing <50 % of the intervention. The final sample thus consisted of 117 participants (71.79 % female, M_{age} = 22.03, SD_{age} = 3.57), of which 57 (48.72 %) were in the mindfulness and 60 (51.28 %) were in the control condition. A power analysis showed that the power for detecting small effects in this sample ($\eta^2 = 0.01$, required sample size for power of 0.80 = 787) was very small, while it was sufficient for medium ($\eta^2 = 0.059$, required sample size for power of 0.80 = 128) and large effects ($\eta^2 = 0.138$, required sample size for power of 0.80 = 52). Demographic information divided per group is listed in Table 1. For analyses involving the physiological data, further data were lost for the following reasons: data files were not saved due to technical difficulties (n = 7; 3 of which were from control condition) and data files with <2 valid startle responses per condition and trial type (cue/ITI) were excluded from the analyses (n = 18; 9 of which were from control condition).

2.2. Procedure

The study involved two lab sessions and completion of a 10-minute intervention at home each day for 12-consecutive days in between lab sessions. Each participant came to the lab separately and was seated in a separate room that was connected to the experimenter room through a door and two-way mirror.

Before the start of the study, each participant received information about the study and provided informed consent. The first session involved completing demographics and a number of questionnaires, followed by a threat-of-shock task. In preparation for the task, electrodes for administration of the electrical stimulus were attached to the distal phalange of the index and middle finger of the non-dominant hand, and electrodes for facial electromyography (EMG) were attached to the center of the forehead (one signal ground electrode) and just underneath the left lower eyelid (two electrodes, one below the outer edge and one below the center of the eye). Headphones were also provided for administration of the startle probes. Then, information about the task and conditions was provided and the threat-of-shock test conducted. Next, the first intervention was delivered in the lab in the form of listening to a 20-minute audiotape. Allocation to conditions was based on order of arrival, with alternating allocation to the control or treatment group. Finally, participants received instructions regarding the homework exercises.

For 12 consecutive days following the first lab session, participants received an email containing the link to the homework exercise each morning. Each day, the 10-minute exercise was followed up with a short questionnaire (two questions each taken from the nonreactivity, nonjudging, and acting with awareness facets of the mindfulness questionnaire). On day 6, participants also received an email with an additional link to a survey containing the full mindfulness questionnaire as well as a question about practice frequency during the first half of the intervention.

Participants then returned to the lab for the second lab session. Similar to the first session, questionnaires were completed and the threat-of-shock task administered. Finally, participants were debriefed, thanked, and could ask any questions they had about the research.

Table 1
Demographic information split per group.

	Mindfulness group (n = 57)	Control group (n = 60)
Sex	Female: 39 (68.4 %)	Female: 45 (75 %)
	Male: 18 (31.6 %)	Male: 15 (25 %)
Age	Range: 18–31	Range: 18–35
	M: 21.91	*M*: 22.13
	SD: 3.186	*SD*: 3.916
Nationality	Dutch: 11(19.3 %)	Dutch: 17 (28.3 %)
	German: 27 (47.4 %)	German: 12 (20 %)
	Other: 19 (33.3 %)	Other: 31 (51.7 %)
Native language	Dutch: 10 (17.5 %)	Dutch: 15 (25 %)
	German: 24 (42.1 %)	German: 13 (21.7 %)
	English: 7 (12.3 %)	English: 2 (3.3 %)
	Other: 16 (28.1 %)	Other: 30 (50 %)

2.3. Questionnaires

2.3.1. Intolerance of uncertainty

One measure that was used to assess intolerance of uncertainty (IU) was the intolerance of Uncertainty Scale – short form (IUS-12; Carleton et al., 2007). It consists of 12 items describing responses to uncertainty in the form of self-statements. These represent two factors: prospective IU (cognitive response facet; 7 items; e.g., "unforeseen events upset me greatly") and inhibitory IU (behavioral response facet; 5 items; e.g., "The smallest doubt can stop me from acting"). A Likert scale ranging from 1 (*not at all characteristic of me*) to 5 (*entirely characteristic of me*) is used to rate identification with the statements. The full score of the scale was used for analysis of the main hypotheses, as recent evidence suggests that a single latent IU factor best represents the construct (e.g., Shihata et al., 2018). Cronbach's alphas suggested that the overall scale showed excellent internal consistency ($\alpha = 0.919$), and the inhibitory ($\alpha = 0.850$) and prospective ($\alpha = 0.891$) subscales showed good internal consistency.

2.3.2. Trait mindfulness

The Five-Facet Mindfulness Questionnaire – short form (FFMQ-sf; Bohlmeijer et al., 2011) was used to assess trait mindfulness. Items are 24 self-statements representing five factors: observing (4 items; e.g., "I pay attention to physical experiences, such as the wind in my hair or sun on my face"), acting with awareness (5 items; e.g., "I do jobs or tasks automatically without being aware of what I'm doing"), describing (5 items; e.g., "I can easily put my beliefs, opinions, and expectations into words"), nonreactivity (5 items; e.g., "I watch my feelings without getting carried away by them"), and non-judging (5 items; e.g., "I make judgments about whether my thoughts are good or bad"). A Likert scale ranging from 1 (*never or very rarely true*) to 5 (*very often or always true*) is used to rate how frequently each self-statement occurred during the past month. For parsimony, the full score was used in the main analyses. This score was computed without items from the observing subscale, as research suggests that this subscale may not be valid in inexperienced meditators (Gu et al., 2016). Cronbach's alpha suggested internal consistency was good (pre $\alpha = 0.879$, post $\alpha = 0.915$).

2.3.3. Panic and phobia

The Albany Panic and Phobia Questionnaire (APPQ; Rapee et al., 1994/1995) was used to assess symptoms associated with social anxiety and panic disorder. Items are 24 short descriptions of symptom-relevant situations corresponding to three subscales: social anxiety (10 items; e.g., "giving a speech"), agoraphobic (9 items; e.g., "going long distances from home alone"), and interoceptive symptoms (5 items; e.g., "exercising vigorously alone"). The situation descriptions are rated on a 9-point Likert scale ranging from 0 (*no fear*) to 8 (*extreme fear*) according to how fear-inducing they would be if encountered during the next week. Cronbach's alpha suggested good internal consistency for the social (pre $\alpha = 0.899$, post $\alpha = 0.898$), and acceptable/good for the agoraphobic (pre $\alpha = 0.779$, post $\alpha = 0.823$) and the interoceptive symptom subscales (pre $\alpha = 0.775$, post $\alpha = 0.834$). Individual subscale scores were used in the analyses.

2.3.4. Worry

The Penn State Worry Questionnaire was used to assess a central symptom of generalized anxiety disorder, worry (PSWQ; Meyer et al., 1990). Items are 16 self-statements describing experience with worrying (e.g., "As soon as I finish one task, I start worrying about everything else I have to do"). The items are rated on a 5-point Likert scale ranging from 1 (*does not describe me*) to 5 (*describes me perfectly*), according to what extent they are true for the participant. Cronbach's alpha suggested that internal consistency was excellent (pre $\alpha = 0.916$, post $\alpha = 0.931$).

2.3.5. Obsessive-compulsive symptoms

The Obsessive-Compulsive Inventory – Revised (OCI-R; Foa et al., 2002). Items are 18 self-statements describing symptom-relevant behaviors and cognitions (e.g., "I repeatedly check doors, windows, drawers, etc."). A Likert scale ranging from 0 (*not at all*) to 4 (*extremely*) is used to rate how much distress the described experience has caused during the past month. Cronbach's alpha suggested good internal consistency (pre $\alpha = 0.887$, post $\alpha = 0.891$).

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

The NPU-threat test was administered using *E*-Prime 2.0 (Psychology Software Tools Inc.) and was adapted from Grillon et al. (2004). To reduce initial startle reactivity, a startle habituation phase was administered preceding the task, consisting of nine presentations of an acoustic startle probe, separated by 10- to 21-second intervals and delivered binaurally through headphones. Also preceding the task, an individual shock workup procedure was used to find a level of electrical stimulation that was perceived as "highly annoying but not painful". The threat test itself consisted of three within-subjects conditions, each presented multiple times throughout the task. During each 2-minute condition, a geometric cue was presented at the center of the screen three times for 8 s, separated by variable inter-trial intervals. Conditions were a no shock (N) condition in which no shock was delivered and the cue was a green circle that therefore had no signal value; a predictable shock (P) condition in which the 100 ms shock was only delivered right before offset of the cue, a red square, with a reinforcement rate of 50 % (i.e., six shocks throughout task); and an unpredictable shock (U) condition, in which the shock was not contingent on cue presence and the cue, a blue triangle, therefore had no signal value. In the U condition, throughout the task, four shocks were delivered during the inter-trial interval (ITI), and two were delivered during cue presence (i.e., six shocks in total). For the duration of each condition, respective additional information about the shock contingencies was also provided at the top of the screen (i.e., "no shock", "shock only during red square", or "shock at any time"). Moreover, per condition, six acoustic startle probes were delivered for the assessment of defensive startle responding via EMG, with three delivered during cue presence and three delivered during the ITI. The task consisted of two recording blocks in which two P and two U conditions were separated by three N conditions in two orders (i.e., PNUNUNP, UNPNPNU), counterbalanced across participants. Following each block, subjective anxiety (assessed separately for cue presence and ITI per condition), as well as intensity, painfulness, and anxiogenic quality of the shock were rated on a 10-point scale ranging from 0 (indicating no response) to 10 (indicating extreme response).

2.4.1. Startle recording and processing

Startle response was recorded using EMG from the orbicularis oculi following published guidelines (Blumenthal et al., 2005). Preceding the recording, the skin was cleaned and the electrodes attached, with a signal ground electrode placed at the center of the forehead and two electrodes placed below the lower eyelid, one below the outer edge and one below the center). Startle probes were delivered binaurally through headphones and were 40 ms, 103 dB bursts of white noise. Prior to the threat test, EMG traces were visually inspected to ensure detectability of startle response. TMSi Polybench was used to measure and record startle blink EMG, and Aphys was used to process startle offline. A 28–1000 Hz band-pass filter was used to filter the raw EMG data. Then it was rectified and filtered using a 40 Hz low-pass filter. Mean and standard deviation of EMG activity during a 200 ms baseline period before startle probe onset and peak startle amplitude within a 20–200 ms period following startle probe onset were recorded and used to determine the startle response. Each trial was individually manually examined as well. If there was excessive noise during baseline, or if the response started before probe onset or within 20 ms of cue onset, the trial was rejected (i.e., scored as missing). On average, 1.12 % of trials were rejected. For all other trials, a threshold of 7 SD above mean EMG activity during baseline was used to determine validity of the startle response with

consideration of baseline EMG activity (cf. Papenfuss et al., 2021). If the response did not cross the threshold, the trial was classified as a non-response trial (i.e., scored as zero). For trials in which the response did cross the threshold (i.e., valid trials), peak amplitude of the first high-frequency response was recorded.

Summary scores to be used in the analyses were then computed from the processed individual responses. First, response amplitude was computed by subtracting mean amplitude during the baseline period from peak startle amplitude. Then, response amplitudes were standardized within subjects using *t* scores to reduce the influence of participants with generally larger startle responses (cf. Nelson and Shankman, 2011). Average startle magnitudes per condition/cue presence were computed within subjects by averaging these standardized responses by condition and cue presence. For the main analysis, average responses were further processed into potentiation scores. Context-potentiated startle was operationalized as the average difference in startle magnitude between the U condition and the N condition ($Context_U = U_{cue+ITI} - N_{cue+ITI}$; cf. Nelson et al., 2016). Fear-potentiated startle was operationalized as the average difference in startle magnitude between the P condition when the cue was present and the corresponding N condition ($Fear_P = P_{cue} - N_{cue}$; cf. Nelson et al., 2016) to investigate the relationship with cued fear.

2.5. Interventions

Audiotapes for both conditions were recorded by author B.D.O., who is a clinical psychologist trained in Mindfulness-Based Stress Reduction (MBSR) with over 15 years of experience teaching MBSR. The duration of the interventions was matched.

2.5.1. Mindfulness with anxiety-specific practice

The mindfulness intervention involved following audio-instructed mindfulness meditation exercises. Specifically, a 20-minute meditation was delivered in the baseline session, and two different 10-minute meditations were delivered on days 1–6 and 7–12, respectively. The 20-minute meditation and the meditation on days 1–6 followed the same basic structure, and the meditation on days 7–12 following a different structure that incorporated a practice of mindfulness toward anxious memories. In the first session, participants were instructed to think of a moderately anxiety-inducing memory for use in the applied practice during days 7–12. Each day of the intervention started with the instruction to commit to the practice for the duration of the audio and to settle into a comfortable but upright position, followed by instructions to pay attention to the breath, focusing on where in the body it is felt most vividly. While focusing on the breath, participants were asked to observe it without trying to control it, and to bring the attention back to the breath when noticing the mind wander. Then, the instructions diverged.

For the practice in-session and on days 1–6, participants were asked to then focus on bodily sensations and thoughts. Specifically, this involved observing these objects of attention, being aware of their qualities and seeing them as observable events rather than getting involved in them, and allowing them to be without having to react to or control them. At the end of the practice on these days, participants were instructed to let go of all specific objects of attention, to be aware of whatever comes into awareness, to notice how it feels, and to allow it to pass.

For the practice on days 7–12, following the breath-focused instructions, participants were asked to recall the moderately anxiety-inducing event previously thought of, to picture the self in the situation, including thinking of associated thoughts and sensations. Similar to the in-session exercise and that of the first six days, this involved observing these objects of attention arise and subside without getting involved in or trying to control them in any way, but this time while picturing the self in that anxiety-inducing situation. At the end of the practice, participants were instructed to let go of the experience and to return the attention to the breath. Participants had the option of going back to the same stressful memory each time, or of choosing a different moderately anxiety-inducing memory if they preferred.

2.5.2. Control

The intervention for the control group involved listening to recordings of excerpts from the book *Harry Potter and the Sorcerer's stone* (J. K. Rowling, 1997). Specifically, a 20-minute recording was delivered during the first session, and 12 consecutive 10-minute recordings were delivered as homework exercises. Before the start of each reading, participants were instructed to commit to listening to the audio, to allow themselves to get absorbed in the story, and, when noticing that their mind has wandered, to bring their attention back to the recording.

2.6. Overview of analyses

Preliminary analyses were conducted using IBM SPSS Statistics 25. The preliminary data analysis included plotting the pattern of startle responding to the NPU-threat test to each combination of condition (N, P,U) and cue presence (cue, ITI) and conducting a 3 (N, P, U) x 2 (cue, ITI) repeated measures ANOVA in order to assess whether the pattern of startle magnitudes was in line with what would be expected based on previous research.

Next, correlations at baseline were inspected in a preliminary analysis to initially cross-sectionally explore the proposed relations pre-intervention as well as the relations between indirect (i.e., from the NPU-threat test) and self-report (i.e., from the IUS) measures of response to uncertainty. Here, a Benjamini-Hochberg sequential adjustment was applied for multiple comparisons, with critical values ranging from <0.001 to 0.05. In preparation for the main analysis, scatterplots of dependent variables post-intervention on pre-intervention with separate lines for the intervention and control groups were examined to determine whether it was necessary to include an interaction effect between dependent variable scores at time 1 (i.e., the covariate) and the intervention group in the ANCOVA mediation model, as ANCOVA assumes parallel lines. Where the lines deviated from parallel, suggesting an interaction, the interaction was included in the model to further investigate whether the assumption of parallel lines was violated. If the interaction was significant, it was included in the model.

The main and mediation analyses were conducted using RStudio. The main effects of treatment on post-intervention outcomes were modeled using separate ANCOVAs, controlling for pre-intervention outcome scores. The post-intervention anxiety symptom measures for social anxiety, agoraphobia, interoceptive fear, worry and obsessive-compulsive symptoms were separately entered as dependent variables, condition was entered as the independent variable, and the respective pre-intervention symptom measures were entered as the covariate. Separate ANCOVAs were also conducted with post-intervention IU and context-potentiated startle as dependent variables, condition as dependent variable, and pre-intervention IU and context-potentiated startle entered as the respective covariate. The mediated effects were modeled using an ANCOVA framework, adjusting for pre-intervention scores on the mediator and outcome variables when estimating the treatment and mediated effects. This approach has been suggested to be the most powerful approach when estimating a mediated effect in pre-post control-group designs (Valente and MacKinnon, 2017). Separate mediation models were estimated for each anxiety outcome (i.e., social anxiety, agoraphobia, interoceptive fear, worry, and obsessive compulsive symptoms) using a latent change score specification within the lavaan package (Rosseel, 2012), constructing latent change scores for the mediator (IU or context-potentiated startle) and outcome variables, respectively. The latent change score specification is based on structural equation models for longitudinal data. A general path diagram for the model without interaction is depicted in Fig. 1, which is based on the model discussed by Valente and MacKinnon (2017) and the more general latent change models presented by McArdle (2009). Change in dependent variables (post- minus pre-intervention) *Y* and change in

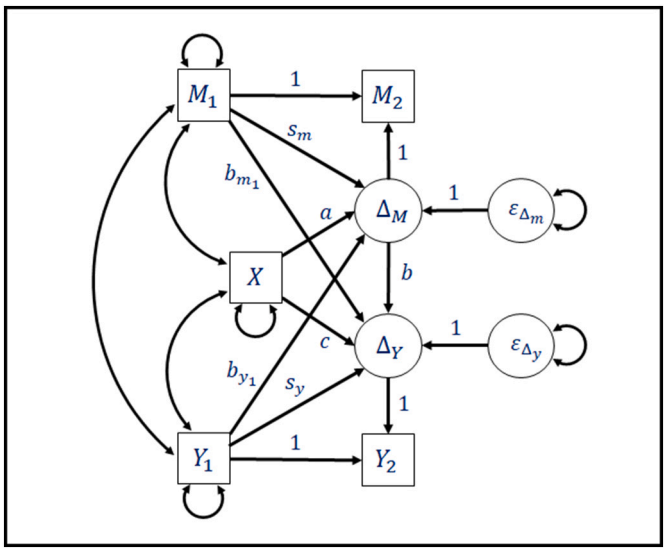

Fig. 1. Path model used for the analysis of the mediation effects. The path model is similar to the model presented by Valente and MacKinnon (2017) (Fig. 2(a)) and models discussed by McArdle (2009). Variable *M* depicts the mediator, *Y* the anxiety symptoms, and *X* the mindfulness intervention. Paths of interest are *a* and *b* (*a*b* gives the indirect effect of *X* on the change in *Y* via *M*) and *c* (the direct effect of *X* on the change in *Y*). To improve readability, parameters for (residual) variances and covariances are not presented (curved arrows).

mediators *M* are modeled as latent (change) scores Δ_Y and Δ_M, respectively. The main effect of the mindfulness intervention (*X*) on the change in anxiety (Δ_Y) is represented by path *c* (direct effect of *X* on Δ_Y), and the mediated effect (indirect effect via Δ_M) is given by *ab*, the product of path *a*, the effect of *X* on the change in the mediator, and path *b*, the effect of the change in the mediator on the change in anxiety. All paths in the diagram were estimated using the lavaan package (Rosseel, 2012), including the mediated effect (not all paths in Fig. 1 were labeled to keep the diagram clear). Where the preliminary analysis suggested, interaction terms representing differences in the effect of the pre-intervention dependent variable between the intervention and control group were included in the path model using the product term XY_1 as measured variable (McArdle, 2009).

3. Results

3.1. Preliminary analyses

3.1.1. Startle response pattern

The pattern of startle responses in the different conditions and during cue presence vs. absence from the NPU-threat test at pre-intervention are plotted in Fig. 2. As can be seen in the figure, startle responses were lowest in the N condition, and there wasn't a notable difference between startle during the ITI and when the cue was present. Furthermore, there was a larger startle response during cue presence in the P condition, noticeably in contrast to the ITI, as would be consistent with a large fear-potentiated startle response. Moreover, the startle responses were overall relatively high in the U condition, with no notable differences between cue presence and ITI, which is consistent with heightened startle potentiated by an unpredictable context. A 3 (N, P, U) x 2 (cue, ITI) repeated measures ANOVA to assess the startle pattern showed main effects for condition, $F(2,107) = 183.95$, $p < .001$, $\eta_p^2 = 0.775$, cue, $F(1,108) = 165.65$, $p < .001$, $\eta_p^2 = 0.605$, and a condition x cue interaction, $F(2,107) = 59.49$, $p < .001$, $\eta_p^2 = 0.527$, which was followed up with separate repeated measures ANOVAs for cued periods and ITIs. For the ITI, the repeated measures ANOVA again showed significant differences in startle magnitudes between conditions, $F(2,216) = 61.28$, $p < .001$, $\eta_p^2 = 0.362$. Pairwise comparisons showed that startle magnitudes were greater in the U condition compared to the P ($p < .001$) and N ($p < .001$) conditions and greater in the P condition compared to the N ($p < .001$) condition. For the cued periods, the repeated measures ANOVA again showed significant differences in startle magnitudes between conditions, $F(2,216) = 142.662$, $p > .001$, $\eta_p^2 = 0.569$. This time, pairwise comparisons showed that startle magnitudes were greater in the P condition compared to the U ($p < .001$) and N ($p < .001$) conditions and greater in the U compared to the N ($p < .001$) condition. These patterns are comparable to what previous applications of the NPU have shown (cf. Schmitz and Grillon, 2012; Papenfuss et al., 2021).

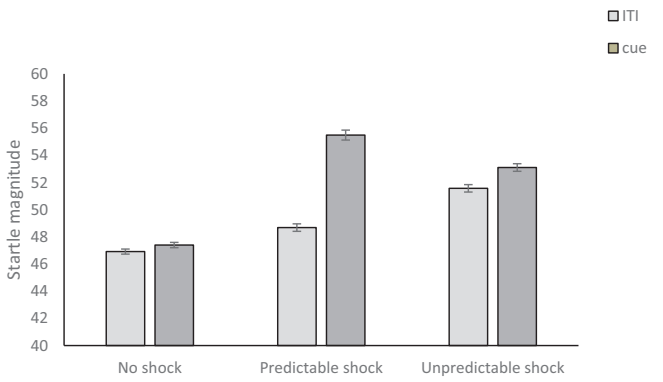

Fig. 2. Startle magnitude per condition and cue presence at pre-intervention assessment. Error bars represent standard error.

3.1.2. Correlation analysis

Pre-intervention bivariate correlations are summarized in Table 2. Trait mindfulness[1] was consistently inversely correlated with anxiety symptom measures, although the strength of associations varied from moderately strong for social anxiety, worry, and obsessive-compulsive symptoms to weaker for interoceptive fear and agoraphobia. Trait mindfulness was also marginally inversely correlated with startle response in the unpredictable shock condition during cue presence. However, it was not significantly related to startle response in the unpredictable shock condition during the ITI, nor was it related to the summary variables assessing context- and fear-potentiated startle. IU was significantly positively related with all anxiety symptom measures, with strong associations with social anxiety, worry, and obsessive-compulsive symptoms and weaker associations with interoceptive fear and agoraphobia. IU was also marginally related to startle in the unpredictable condition during cue presence, while the inhibitory subscale was significantly related to startle in the unpredictable condition during cue presence. To assess whether inhibitory IU was specifically related to startle during the cue in the unpredictable condition beyond individual differences in anxiety symptoms, partial correlations were explored when controlling for anxiety symptoms. Here, inhibitory IU demonstrated specificity in predicting startle in the cued unpredictable condition when controlling for social anxiety ($r_{\text{IU-startle}} = 0.260$; $p = .007$), agoraphobia ($r_{\text{IU-startle}} = 0.235$; $p = .014$), interoceptive fear ($r_{\text{IU-startle}} = 0.259$; $p = .007$), and worry ($r_{\text{IU-startle}} = 0.227$; $p = .018$), but not when controlling for obsessive compulsive symptoms ($r_{\text{IU-startle}} = 0.152$; $p = .117$). In contrast, neither the overall IU score nor its subscales were significantly related to startle response during the ITI or context- or fear-potentiated startle.

[1] In response to a comment by an anonymous review, the analyses were repeated with the items of the observe subscale included in the total mindfulness score. The results showed that the addition did not change the correlation findings.

Table 2
Bivariate correlations between all variables at baseline.

	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.
1. FFMQ-O	–												
2. IUS-P	−0.436**	–											
3. IUS-I	−0.506**	0.720**	–										
4. IUS	−0.499**	0.953**	0.896**	–									
5. APPQ-S	−0.533**	0.446**	0.463**	0.487**	–								
6. APPQ-A	−0.264**	0.292**	0.219*	0.283**	0.469**	–							
7. APPQ-I	−0.318**	0.314**	0.283**	0.324**	0.446**	0.678**	–						
8. PSWQ	−0.552**	0.473**	0.470**	0.508**	0.418**	0.331**	0.193()	–					
9. OCI-R	−0.489**	0.547**	0.525**	0.578**	0.469**	0.362**	0.325**	0.424**	–				
10. St U_{cue}	−0.196(*)	0.158	0.231*	0.202(*)	−0.005	0.003	−0.065	0.060	0.198(*)	–			
11. St U_{ITI}	0.018	0.142	0.108	0.139	0.013	0.155	0.185	0.039	0.054	0.110	–		
12. $Context_U$	−0.065	0.126	0.172(*)	0.156	0.014	0.092	0.045	0.002	0.067	0.638**	0.727**	–	
13. $Fear_P$	0.029	−0.127	−0.060	−0.108	0.022	0.031	−0.061	−0.084	−0.171	−0.025	0.211(*)	0.423**	–

Correlations derived from final sample ($N = 117$). FFMQ-O = sum score of five facet mindfulness questionnaire without observe subscale, IUS = intolerance of uncertainty scale, IUS-P = prospective subscale, IUS-I = inhibitory subscale, 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, St U_{cue} = Startle during the cue presence of the unpredictable shock condition of the NPU, St U_{ITI} = Startle during the ITI of the unpredictable shock condition of the NPU, $Context_U$ = summary score – context-potentiated startle, $Fear_P$ = summary score – fear-potentiated startle. Correlations corrected for multiple comparisons using the Benjamini-Hochberg sequential adjustment. * < 0.05, ** < 0.01, (*) < 0.1.

3.2. Hypothesis testing

3.2.1. Intervention effects

To investigate hypotheses (I) and (II), ANCOVAs were conducted for each of the anxiety symptom measures (i.e., social anxiety, agoraphobia, interoceptive fear, worry), and obsessive-compulsive symptoms and both self-report IU and context-potentiated startle. Raw and descriptive statistics for each outcome variable are summarized in Table 3 (columns a and b). Adjusted means based on the ANCOVAs are summarized in column c of Table 3.

Regarding hypothesis (I), for social anxiety symptoms, the homogeneity of regression slopes assumption was found to be violated based on a significant medium-sized interaction effect between condition and pre-intervention symptom scores, $F(1,112) = 7.851$, $p = .006$, partial $\eta^2 = 0.066$. The interaction effect was thus kept in the model. To follow up on the significant interaction effect, predicted means for both groups were estimated at different pre-intervention symptom levels, specifically at lower levels ($M - 1SD$) and at higher levels ($M + 1SD$). Results showed that for low pre-intervention social anxiety levels, the predicted post-intervention social anxiety symptom mean was significantly higher for the mindfulness (11.586) than for the control group (7.432). In contrast, for high pre-intervention symptom levels, there was a trend for the predicted post-intervention social anxiety symptom mean to be lower for the mindfulness (24.803) than for the control group (28.491). Counter to expectations, for agoraphobia, $F(1,113) = 0.531$, $p = .467$, partial $\eta^2 = 0.005$, interoceptive fear, $F(1, 113) = 0.003$, $p = .954$, partial $\eta^2 = 0.000$, worry, $F(1, 113) = 0.155$, $p = .695$, partial $\eta^2 = 0.001$, and obsessive compulsive symptoms, $F(1, 113) = 0.018$, $p = .893$, partial $\eta^2 = 0.000$, the main effects of condition were small and non-significant. As can be seen in Table 3, estimated marginal means post-intervention were very close together for both conditions on these outcomes.

Concerning hypothesis (II), for IU, a small, marginally significant main effect of condition was found, $F(1, 113) = 3.873$, $p = .052$, partial $\eta^2 = 0.033$, with the estimated marginal mean being slightly lower for the mindfulness group (See Table 3). Counter to expectations, for context-potentiated startle, the main effect of condition was small and non-significant, $F(1, 91) = 0.311$, $p = .578$, partial $\eta^2 = 0.003$. As can be seen in Table 3, estimated marginal means post-intervention were close together for both groups, with the estimated mean being slightly lower for the mindfulness group.

Table 3
Means and standard errors at pre- and post-intervention assessment points, as well as adjusted post-intervention means.

Outcome	Condition	(a) Pre-intervention			(b) Post-intervention			(c) Post-intervention (adjusted)	
		Range	*M*	*SD*	Range	*M*	*SD*	*M*	*SE*
APPQ-SP	C	4–57	23.850	12.307	1–55	19.458	12.713	17.829	0.900
	M	0–58	20.632	12.838	0–39	17.333	9.877	17.754	0.880
APPQ-AG	C	2–37	18.733	8.034	0–42	16.085	9.420	16.871	0.786
	M	4–55	20.737	10.251	3–43	18.386	9.662	17.366	0.769
APPQ-IN	C	0–26	5.233	5.595	0–22	4.864	5.560	5.147	0.388
	M	0–30	5.842	6.256	0–27	5.298	6.310	5.145	0.379
PSWQ	C	33–75	57.717	10.069	31–76	54.288	11.743	51.198	0.897
	M	22–75	52.386	13.104	18–71	48.930	13.130	50.054	0.878
OCI-R	C	3–49	20.983	10.608	5–40	18.170	9.914	17.197	0.710
	M	2–55	19.018	12.075	2–45	16.263	11.138	16.854	0.695
IUS	C	13–49	30.133	9.081	14–46	28.695	8.722	27.961	0.615
	M	12–51	29.228	10.760	12–47	25.965	8.789	25.937	0.601
$Context_U$	C	−5.21–27.58	10.745	6.700	−5.71–21.71	7.583	6.359	7.494	0.910
	M	−2.97–28.35	9.947	6.779	−7.79–25.53	6.211	6.488	6.767	0.929
$Fear_P$	C	−2.32–18.97	9.005	5.078	−3.14–19.24	6.054	5.639	5.800	0.780
	M	−3.95–17.65	7.098	4.902	−5.5–16.57	5.462	5.113	5.670	0.797

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, $Context_U$ = summary score – context-potentiated startle, $Fear_P$ = summary score – fear-potentiated startle, Groups: M = Mindfulness ($n_{pre} = 57[52]$; $n_{post} = 57[50]$), C = Control ($n_{pre} = 60[57]$; $n_{post} = 59$ [48]), numbers in [] = n for conditioning task data.

3.2.2. Mediation effects

The results from the mediation analyses evaluating IU as mediator while controlling for baseline levels of both IU and the respective anxiety questionnaire are summarized in Table 4. The paths in the table correspond to the paths in the path model displayed in Fig. 1. Again, for social anxiety, the interaction effect was included in the model. The mediation analyses revealed that for social anxiety symptoms, the coefficients indicate that the mindfulness intervention was associated with a significant increase in IU, which in turn was associated with an increase in symptoms, meaning that the mediated effect was in turn also positive. However, these coefficients are not very informative as they are estimated at a pre-intervention symptom score of zero. The interaction effect, which is negative and significant, means that for every unit increase in pre-intervention symptom levels from zero, the symptom-increasing direct effect of treatment decreases. Similarly, the mediated effect of the intervention, which is also negative and significant, means that for every unit increase in pre-intervention symptom levels, the indirect effect decreases as well. This means that, at average values of pre-intervention symptom levels, the direct effect becomes small and non-significant (at mean pre-intervention symptom levels: 22.28; path c: 6.295–22.28 * 0.225 = 1.282), while the mediated effect becomes negative and significant (mediated effect: 1.936–22.28 * 0.135 = −1.072), meaning that for average pre-intervention symptom levels, the mindfulness intervention showed a significant indirect effect on decreased anxiety symptoms through IU.

Mediation analyses for the other outcome variables without interaction effects revealed that the mindfulness intervention was associated with a significant decrease in IU (path a), with change in IU being positively associated with change in anxiety symptoms for all outcome variables (path b). The test of the mediated effect showed that the intervention significantly indirectly decreased anxiety symptoms through IU for worry and marginally indirectly decreased symptoms through IU for agoraphobia and obsessive-compulsive symptoms (*ps* < 0.07). However, the mediated effect was not significant for interoceptive fear.

The direct effect of the treatment on anxiety symptoms was not significant for any of these outcomes (path c). Only the effect of treatment on agoraphobia symptoms reached marginal significance. It should be noted that the direct effect, when IU and pre-intervention symptom levels were accounted for in the model, although non-significant, was positive and thus in the opposite direction than would be expected for all outcomes. Importantly, however, the total effect was negative and it only was positive when pre-intervention symptom levels were included, which explain the majority of the variation, as well as mediator levels at pre- and post-intervention, leaving little variation to be explained by condition. The vast majority of participants exhibiting low pre-intervention symptom levels means that not much improvement is possible, thus leading to chance differences in post-intervention symptom levels by condition, which in this case turned out to be positive, yet small and mostly non-significant (see Fig. 3).

The results for the analysis evaluating context-potentiated startle as a mediator are summarized in Table 5. The analysis revealed that the intervention was not associated with change in context-potentiated startle (path a) and that change in startle was not associated with change in symptom levels (path b). Hence, the mediated effect of the intervention on symptoms through context-potentiated startle was non-significant for all outcome variables. Here too, the direct effect of treatment on anxiety symptoms was not found to be significant for any of the outcomes (path c). All of the parameters in the model had standard errors that were comparatively large.

Table 4
Results of the mediation analysis for IU as mediator.

Outcome	Path a	Path b	Path c	Med. effect
APPQ-S[(i)]	3.720(1.881)**	0.520(0.166)**	6.295(2.616)*	1.936(1.097)(*)
APPQ-A	−1.944(0.958)*	0.468(0.102)**	1.838(1.070)(*)	−0.910(0.490)(*)
APPQ-I	−1.967(0.950)*	0.137(0.056)*	0.245(0.583)	−0.270(0.171)
PSWQ	−2.066(0.978)*	0.721(0.116)**	0.800(1.248)	−1.491(0.745)*
OCI-R	−1.839 (0.953)(*)	0.512(0.095)**	0.792(0.995)	−0.942(0.519)(*)

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.
* < 0.05, ** < 0.01, (*) < 0.1.
[i] Model includes interaction; interaction effect = −0.225(0.113)*; mediated effect through interaction = −0.135(0.057)*.

4. Discussion

The aim of the present study was to investigate whether a mindfulness intervention would reduce response to uncertainty and anxiety symptoms. Based on the finding that response to uncertainty plays a central role in anxiety and represents a potentially important treatment target, a mindfulness-based approach may be well-suited to the treatment of anxiety. Specifically, mindfulness practice should reduce aversive responses to uncertainty. Instead, it should promote acceptance of uncertain aspects of experience, foster a focus on the present moment, and concomitantly increase the ability to cope with unpleasant aspects of experience such as uncertainty. Building on a previous small cross-sectional investigation of mindfulness, anxiety symptoms, intolerance of uncertainty and physiological response to uncertainty by Papenfuss et al. (2021), the present study was designed to examine these relations in a larger sample and with an experimental design. We hypothesized that, compared to a control intervention, a mindfulness intervention should (I) reduce symptoms of anxiety and (II) decrease response to uncertainty, as measured by both self-reported IU and context-potentiated startle in the NPU-threat test. Finally, we hypothesized that (III) reductions in anxiety symptoms should be mediated by these measures of response to uncertainty. The study also examined the relations between self-reported IU and startle in the context of uncertainty, as well as relations with mindfulness and anxiety symptoms at baseline.

The hypotheses were partially supported by the data. Although pre-intervention relations between trait mindfulness and anxiety symptoms were consistently negative and significant, concerning hypothesis (I), a significant main and interaction effect of the intervention was only found for social anxiety symptoms – i.e., for higher pre-intervention symptom levels, estimated post-intervention symptom means were lower for the mindfulness group compared to the control group. For the other anxiety symptom variables, no main or interaction effects of the intervention were found. Furthermore, although pre-intervention bivariate correlations showed a strong inverse relation between trait mindfulness and IU, in terms of hypothesis (II), the effect of the intervention on IU was only marginally significant. In contrast, no such effect of the mindfulness intervention was found on context-potentiated startle and context-potentiated startle was also not significantly related to mindfulness pre-intervention. Finally, regarding hypothesis (III), the mediation models revealed that the mindfulness intervention significantly decreased symptom levels of social anxiety and worry indirectly through change in IU, and marginally so for agoraphobia and obsessive-compulsive symptoms. No evidence of a mediated effect through IU was found for interoceptive fear. Counter to expectations, no significant effects were found in the mediation model evaluating context-potentiated startle as mediator.

The non-significant main effects of the intervention on the majority of anxiety outcomes could be due to a number of factors. First, following methods typical in experimental psychopathology, we employed a relatively low-intensity intervention and evaluated the effects in an unselected non-clinical sample (Waters et al., 2017). Both elements may

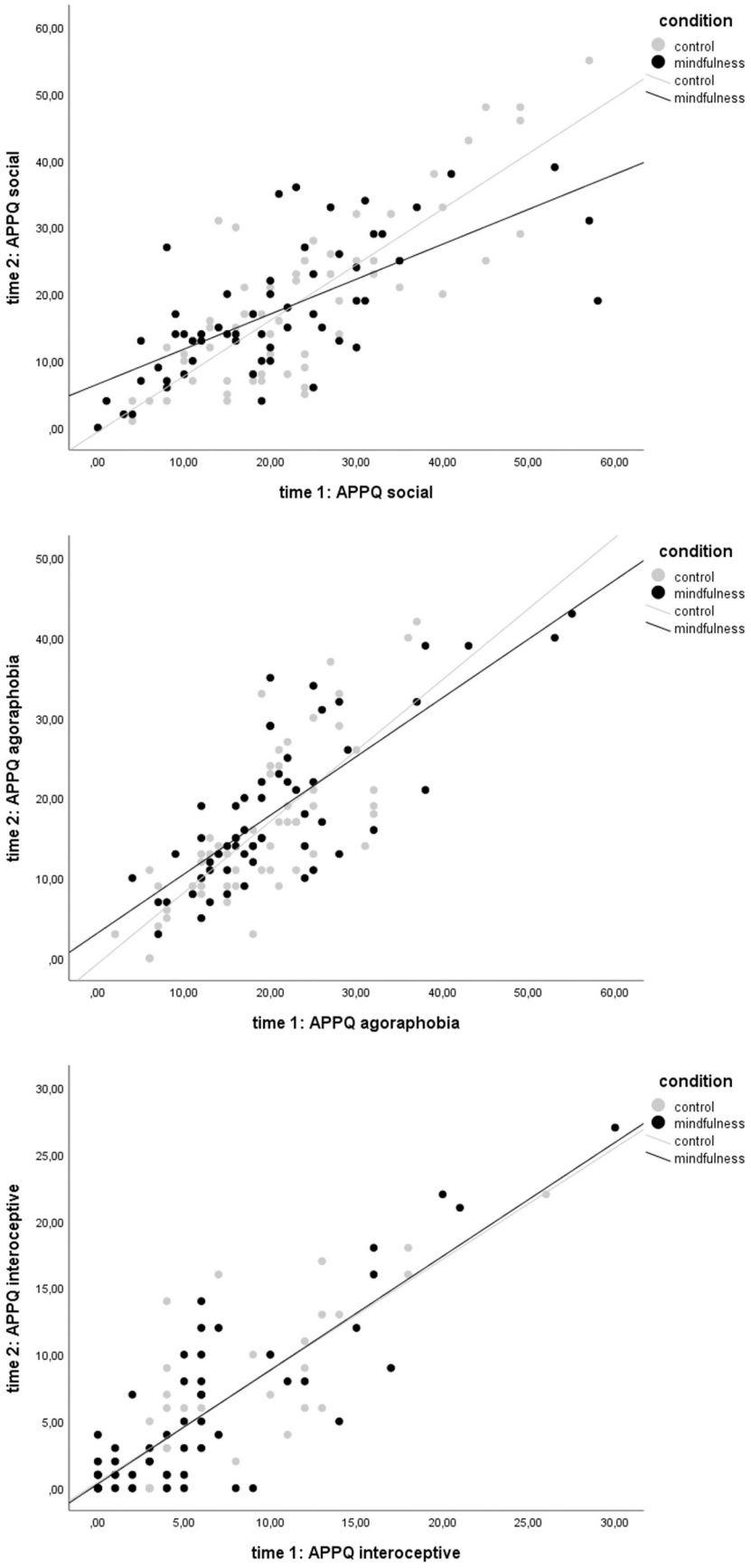

Fig. 3. Scatterplots of post-intervention symptom levels on pre-intervention symptom levels, with separate fit lines per intervention and control group. APPQ = Albany panic and phobia questionnaire, PSWQ = penn state worry questionnaire, OCI-R = obsessive compulsive inventory – revised.

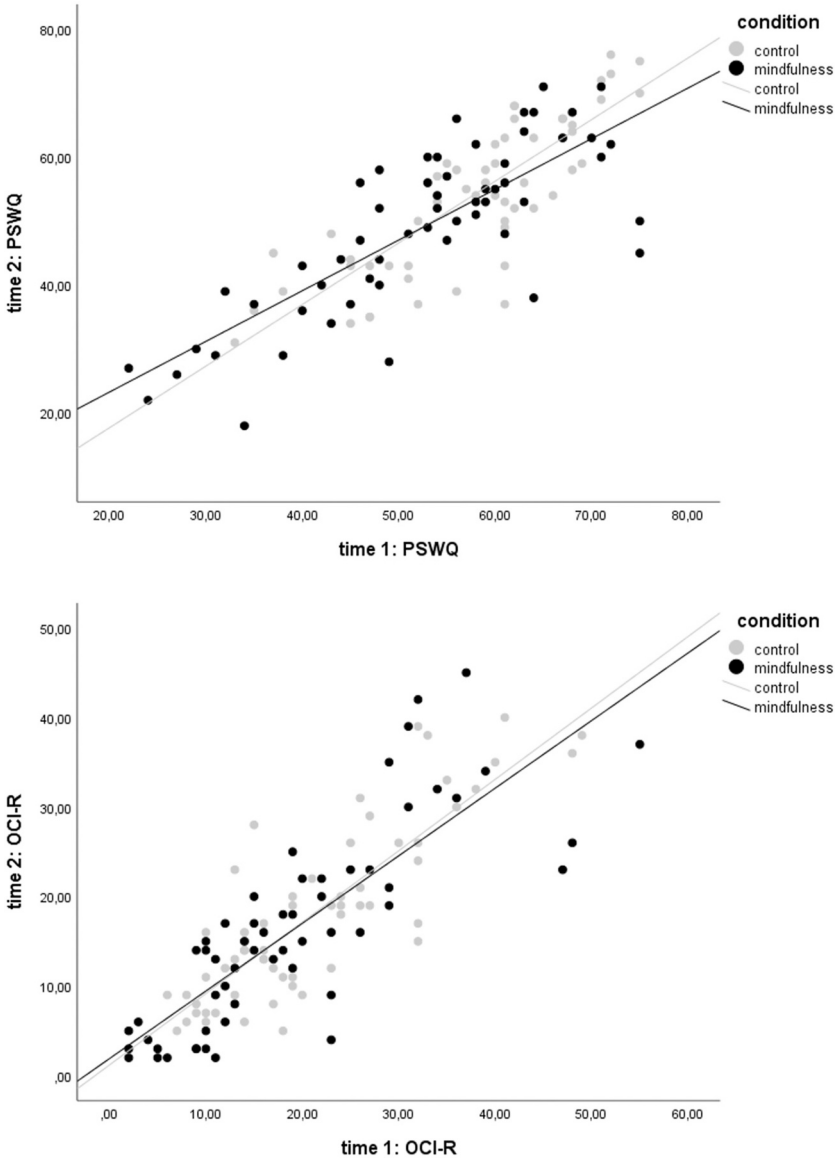

Fig. 3. (*continued*).

Table 5
Results of the mediation analysis for context-potentiated startle as mediator.

Outcome	Path a	Path b	Path c	Med. effect
APPQ-S[(i)]	3.256(2.661)	0.007(0.135)	9.306(3.152)*	0.023(0.570)
APPQ-A	−0.571 (1.293)	−0.018 (0.105)	0.826(1.324)	0.010(0.064)
APPQ-I	−0.747 (1.284)	−0.026 (0.054)	−0.225 (0.669)	0.020(0.052)
PSWQ	−0.716 (1.305)	−0.061 (0.131)	−0.814 (1.656)	0.044(0.123)
OCI-R	−0.709 (1.282)	0.109(0.104)	0.120(1.289)	−0.077 (0.157)

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.
* < 0.05, ** < 0.01, (*) < 0.1.
[i] Model includes interaction; interaction effect = −0.413(0.134)*; mediated effect through interaction = −0.001(0.027).

have hampered our ability to detect significant main effects: the intervention may have been too brief to significantly affect anxiety levels and the sample may have exhibited anxiety levels that were too low to enable them to benefit from such a brief intervention. The significant interaction effect for social anxiety corroborates this argument, as the predicted anxiety symptom levels were lower in the mindfulness group compared to control when pre-intervention symptom levels were higher. Moreover, as can be seen in Fig. 3, for most of the symptom measures, the majority of participants exhibited low levels of anxiety, leaving little room for improvement. A second explanation may be due to the control intervention instructions. The control intervention consisted of listening to a Harry Potter audio reading. As the participants in the present sample were in their early 20s, a generation that grew up with the Harry Potter book series, this particular book may have carried substantial meaning to many of the participants, possibly enabling them to delve into peaceful and comfortable memories, thereby causing relief from anxious thoughts. Indeed, fictional audiobooks have previously been shown to be related to increased meaning in life (Poerio and Totterdell, 2020), which in turn has been shown to be inversely related to anxiety (Ostafin et al., 2021). In addition, listening to audiobooks has been shown to foster relaxation and to cause distraction from anxiogenic circumstances (Best et al., 2020), both of which may lead to decreased

anxiety levels. Further, there is some similarity between the control and mindfulness conditions in that they both involved the volitional direction of attention. This could mean that, with the intervention being rather short, the differences between intervention effects were not large enough to be detected. Presumably, with higher intervention intensity, differences between the treatments would be more pronounced. In sum, although the experimental psychopathology approach has the advantage of enabling exploration of proposed effects in relatively low-cost studies before conducting larger more costly studies, together with a strong control intervention this choice of methods may have limited our ability to find significant main effects on most of the anxiety outcomes.

Regarding the indirect effect of the intervention on anxiety symptoms through IU, the findings corroborate and extend the existing evidence for the potential mechanistic role of IU in the relationship between mindfulness and anxiety. Previous experimental studies demonstrating an effect of mindfulness practice on IU have not examined the mediating role of IU for anxiety symptoms (Mathur et al., 2021; Victorson et al., 2017) and previous research demonstrating a mediating role of IU has been limited to cross-sectional designs (Kraemer et al., 2016; Papenfuss et al., 2021). To our knowledge, this study is the first to demonstrate a mediating role of IU for the effect of mindfulness practice on anxiety in an experimental setting. Although a significant effect was found only for social anxiety and worry symptoms, a marginally significant and thus potentially meaningful mediation effect was also found for agoraphobia and obsessive-compulsive symptoms. Given the overall limitations of the design, these significant mediation findings and otherwise consistent direction of the marginally significant mediation effects warrant additional research exploring these relationships.

In contrast, the present study found no evidence for a mediation role of physiological response to uncertainty in the relationship between mindfulness practice and anxiety symptoms. The correlation analyses similarly suggested no relation between context-potentiated startle and trait mindfulness or anxiety. The only significant correlation with the physiological measure was between average startle response in the unpredictable condition of the NPU when a cue was on the screen and the inhibitory subscale of the IU (startle in the cued unpredictable condition also showed marginally significant positive associations with the total IU score and inverse associations with trait mindfulness and context-potentiated startle also showed a marginally significant positive association with inhibitory IU). These findings are in contrast to those reported in a previous smaller cross-sectional study investigating the mediating role of physiological response to uncertainty in the relation between mindfulness and anxiety: In the previous study, the relation between both IU and inhibitory IU with context-potentiated startle was found to be negative and non-significant (Papenfuss et al., 2021).

One explanation for the mostly non-significant findings may lie in the large variability of the startle responses (see Table 3 for descriptive statistics). There may be too many factors affecting startle response to allow for the detection of reliable relationships in this relatively small sample. In addition, the intensity of the intervention may have been too low to cause a significant change on a physiological level. Moreover, due to technical difficulties, we were not able to obtain physiological data from all participants, further limiting the power to detect small effects Finally, it may be that although there seems to be some relation between startle response in the context of unpredictable threat and IU, the two measures may not tap the same underlying emotional processes regarding uncertainty. Instead, they may assess different levels of processing, with startle representing a lower-level defensive response and IU reflecting a higher level cognitive process. It has been argued that such different-level processes do not necessarily have to contribute to the same conscious emotional state (cf. LeDoux and Hofmann, 2018). Nevertheless, the cross-sectional results of the present study demonstrated a marginally significant inverse relationship between trait mindfulness and startle under the condition of uncertain threat, and thus suggests that the relation between mindfulness and physiological response to uncertainty should be further explored in future research.

In the context of previous studies evaluating the relationship between IU and startle response under conditions of unpredictable threat, the findings of the present study add more variability to the already mixed nature of previous findings. Specifically, although some studies have shown a positive relation between startle during periods of unpredictable threat and IU (Chin et al., 2016), others have shown no relation (Bennett et al., 2018; Papenfuss et al., 2021), and others have shown a negative relation (Nelson and Shankman, 2011) or opposite relations with the different facets of IU (specifically, a positive relation with prospective and a negative relation with inhibitory IU; Nelson et al., 2016). Furthermore, other studies have demonstrated a relation between IU and startle during conditions of certain safety from shock. This may point to the possibility that IU may be related to a bias favoring generalization of aversive physiological responding to safe conditions in the context of threat of shock (Morriss et al., 2021a).

The present study provides some evidence in favor of a positive relation between startle in response to uncertain threat and IU, with the strongest relations demonstrated with the inhibitory facet of IU. The inhibitory facet also demonstrated specificity in predicting startle when controlling for individual differences in anxiety symptoms. Inhibitory IU did not predict startle when controlling for obsessive compulsive symptoms, which may be due to the particularly large correlation between the two individual difference measures. This finding of a positive relation between startle in response to uncertain threat and IU seems to be in direct contrast to the findings by Nelson et al. (2016), and the generally mixed findings call for more research on how and under what conditions IU manifests in physiological responses to uncertain threat.

For instance, there have been numerous methodological differences in the nature of the unpredictability or operationalization of response to unpredictable threat in these studies. For instance, some studies have examined relations of IU with average startle response per condition and cue presence (cf. Bennett et al., 2018), while others have examined relations with composite scores (cf. Chin et al., 2016). These scores are formed by subtracting average startle of a more neutral condition (such as the no shock condition or the intertrial interval between cue presentations) from average startle response of the condition of interest, to capture startle potentiation. Also in this calculation of composite scores, different responses have been used depending on operational definition of response to uncertain threat, either using separate averages for periods of cue presence/absence (cf. Nelson and Shankman, 2011) or using the average startle response across cue conditions (cf. Nelson et al., 2016; Papenfuss et al., 2021). It is not common that results for both average responses and potentiation scores are reported. In the present study, for the bivariate correlations both average responses per cue presence as well as context-potentiation were examined, with diverging results, as correlations with potentiation scores were not significant. Thus, the significant correlation between inhibitory IU and startle during cue presence in the unpredictable shock condition cannot easily be interpreted or embedded within previous research findings. It should be noted that the use of difference scores in correlational analyses has been criticized as difference scores are subject to a loss of potentially important information and have been argued to be less reliable than their individual parts (Cohen and Cohen, 1983; Griffin et al., 1999). Thus, future studies are needed that investigate how these methodological decisions influence findings.

Another methodological consideration concerns the uncertainty instructions used in the NPU task. Participants were instructed with information concerning the predictability of the electrical stimulus on the screen during the unpredictable shock condition, which may reduce the perceived uncertainty and may thus render the uncertainty manipulation too weak to affect IU-related responses. Indeed, previous research using uninstructed classical threat conditioning tasks has more reliably shown relations between psychophysiological responding and IU (Morriss et al., 2021c). For instance, during uninstructed threat extinction, the extinction phase follows a fear acquisition phase, in which the association between shock and a stimulus is learned. The uninstructed

nature of the extinction phase means that at the beginning of the extinction phase, the association between shock and stimulus is unknown, which maximizes uncertainty Research on uninstructed threat extinction using skin conductance responses has demonstrated that individuals high in IU exhibit impaired threat extinction, suggesting difficulties with the updating of threat and safety associations under conditions of uncertainty (Morriss et al., 2021b). In sum, these considerations may mean that the NPU may not be the ideal task to examine individual differences in physiological responding to uncertainty and thus future research is needed examining these relations in threat of shock studies in which uncertainty is maximized, for instance by using uninstructed shock contingencies.

4.1. Limitations and future research

There are several other limitations in addition to those mentioned above. Of the initial sample of participants, 22 % were excluded from the analysis due to a lack of adherence by completing less than the required 50 % of the interventions. This means that the sample was relatively small, which limits the power to detect small effects. Moreover, the participants may not have been intrinsically motivated to participate in the intervention, as participants may have been more motivated by the course credit they received for their participation. Lower intrinsic motivation for the mindfulness practices may have limited effectiveness of the intervention. Both of these limitations can be addressed with design adjustment in future studies. For instance, patients with heightened anxiety may be recruited in order to address these issues. Another limitation is that previous engagement with mindfulness practice was not assessed in the present study, which may be a confounding factor influencing between-group differences. This, too, can be addressed in future studies by ensuring that groups do not differ regarding previous experience with mindfulness practice.

Despite these limitations, the present study also had important strengths. To our knowledge, this was the first study exploring the mediating role of IU for the effect of mindfulness on anxiety symptoms in an experimental setting. Such research is crucial for better understanding the malleability of IU and contributes to recent research examining the usefulness of other types of experimental interventions in reducing IU-related anxiety (e.g., Oglesby et al., 2017; Morriss et al., 2020). Moreover, we employed a statistical analysis method based on ANCOVA for the evaluation of the mediation effect that enables taking into account pre-intervention differences in mediator and outcome variables. This approach has been argued to be the most powerful analysis method as investigated in simulation research comparing multiple methods of assessing the mediated effect in the pre-post control group design (Valente and MacKinnon, 2017). Furthermore, although the sample size used was not ideal, it is still a strength, as it was larger in comparison to most of the past studies on the topic (e.g., Papenfuss et al., 2021; Nelson and Shankman, 2011) Although we did not detect the expected main effects, IU emerged as a significant mediator of the effect of the mindfulness intervention on anxiety symptoms. Future studies should further explore these relationships in participants that are higher in anxiety and with higher-intensity interventions.

Open science disclosure

The authors confirm that all measures, conditions, and data exclusions, as well as sample size determination have been reported in this manuscript.

Ethical standards

The study has been approved by the appropriate ethics committee and has therefore been conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Participants gave their informed consent prior to inclusion in the study.

Declaration of competing interest

The authors declare that they have no conflict of interest.

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